2009

New Developments in Xanthate Ester Chemistry and the Potential for Protecting Group Applications

Matthew Hobson Jones
College of William & Mary - Arts & Sciences

New Developments in Xanthate Ester Chemistry and the Potential for Protecting Group Applications

Matthew Hobson Jones

Heathsville, Virginia

B.S., College of William and Mary

A Thesis presented to the Graduate Faculty
of the College of William and Mary in Candidacy for the Degree of
Master of Science

Department of Chemistry

The College of William and Mary
January 2009

APPROVAL PAGE

This Thesis is submitted in partial fulfillment of
the requirements for the degree of

Master of Science

Matthew Hobson Jones

Approved by the Committee, January 2009

Committee Chair
Professor Christopher Abelt, Chemistry
The College of William & Mary

Associate Professor Robert Hinkle, Chemistry
The College of William & Mary

Assistant Professor Elizabeth Harbron, Chemistry
The College of William & Mary

ABSTRACT PAGE

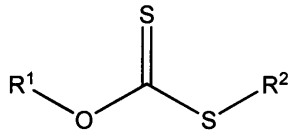
Xanthates are an important and unique class of compounds that have proven to be useful in a wide variety of industrial and synthetic applications. Xanthates may also prove to be an important addition to the rapidly expanding field of protective group chemistry. The focus of this thesis is to determine the potential of the xanthate ester functional group to serve as an effective alcohol protective group. An extensive review of literature reveals promising results and includes a thorough compilation of protective, deprotective, and transformative reactions for xanthate protected alcohols. Additionally, new and relevant developments are reported. These include: some general obstacles of xanthate synthesis, the transformation of xanthate protected alcohols to alkyl halides via the Vilsmeier reagent, and a single step protection of alcohols by way of an acylation reaction with alkyl bromodithioformates.

Table of Contents

Xanthate Esters

In the past half century the field of synthetic organic chemistry has seen a period of rapid growth. This progression is especially evident in the area of drug development, where the multi-step synthesis has evolved from a simple stepwise process into an art-form of creative ingenuity and maximal efficiency.[1] Protective groups, in particular, are instrumental in this process because they provide chemists with a temporary method to conserve certain regions of a substrate, while modifying others.[2] This report will discuss past and current developments in xanthate ester chemistry, as well as explore the viability of the xanthate ester moiety (Figure 1) to serve as an effective protective group. Additionally, newly discovered and relevant protective/deprotective methods developed in the Abelt lab will also be discussed.

Figure 1: Xanthate Ester

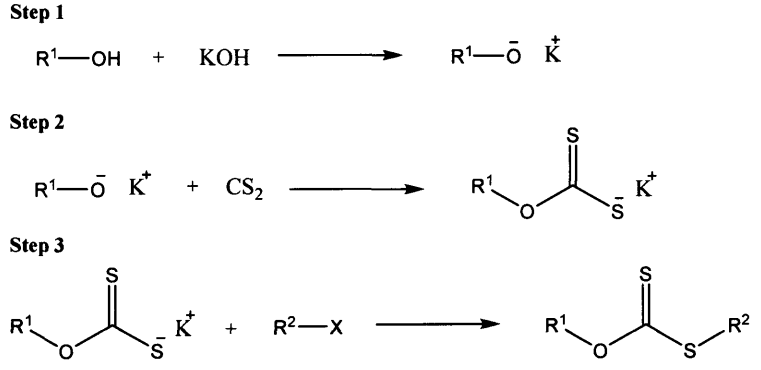


Xanthate Ester
(*O,S*-Dialkyl dithiocarbonate)

Xanthate esters, also known as *O,S*-dialky dithiocarbonates, are yellow foul smelling compounds that are useful in a variety of chemical processes. The conventional method of xanthate synthesis involves the use of xanthate salts, which have been know since 1822.[3] These salts are easily prepared from the nucleophilic addition of an alkoxide to carbon disulfide. The corresponding xanthate ester is then produced by treating the xanthate salt with an alkyl halide in conditions favorable to an S_N2 displacement reaction.

Shown below in Figure 2 is a three step reaction scheme for the conventional synthesis of xanthate esters.

Figure 2: Conventional Xanthate Ester Synthesis



If the alcohol, R^1OH, is an intermediate substrate in a complex multi-step synthetic procedure, then the reaction scheme above can be described as a protective procedure for the alcohol functionality.

Structurally xanthate esters and their thiolate analogs share a close similarity to the ester form of carbonic acid (see Figure 3). However, their chemical properties are markedly different. This variation is largely due to the C=X (X = O or S) double bond, and its effect on the polarization and overall stability of the molecule. The thiocarbonyl double bond (C=S) is longer, softer, and weaker in comparison to the strongly polar and more stable carbonyl (C=O).[4] One notable distinction is that the sp^2 carbon of the thiocarbonyl is more electrophilic than that of the carbonyl.[5] Moreover, recent experimental studies in this lab also indicate that the sulfur at the opposite end of thiocarbonyl has a substantial nucleophilic character as well.[6] One final and important observation, attributable to the relative stabilities of the central C=X bond, is the propensity for the thiocarbonyl containing diesters, *O,S*-dialkyl-xanthates and *O,O*-dialkyl-

thiocarbonates, to rearrange in relatively mild conditions to form their more stable carbonyl containing isomers, *S,S*-dialkyl-dithiocarbonates[7, 8] and *O,S*-dialkyl-thiocarbonates.[9]

Figure 3: Rearrangement of Thiocarbonyl Containing Diesters[7,8,9]

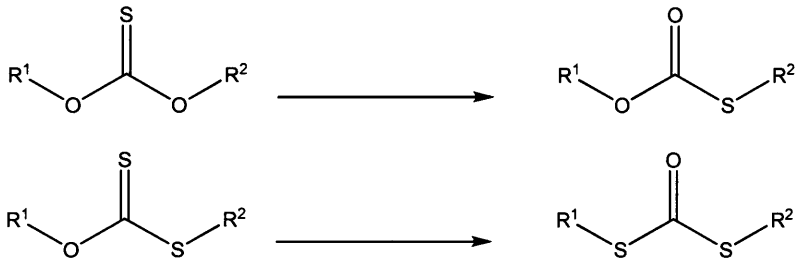
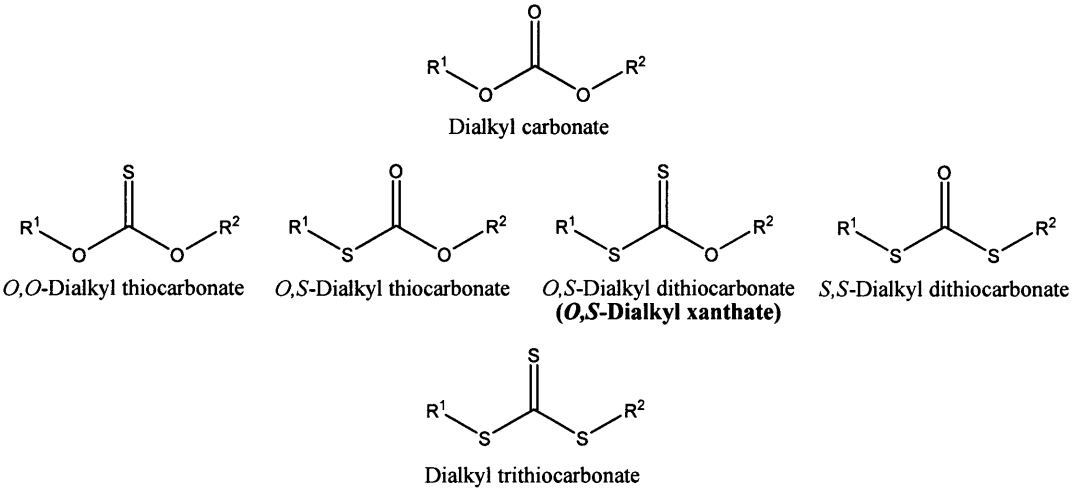


Figure 4: Dialkyl-carbonate and its Thiol Analogs



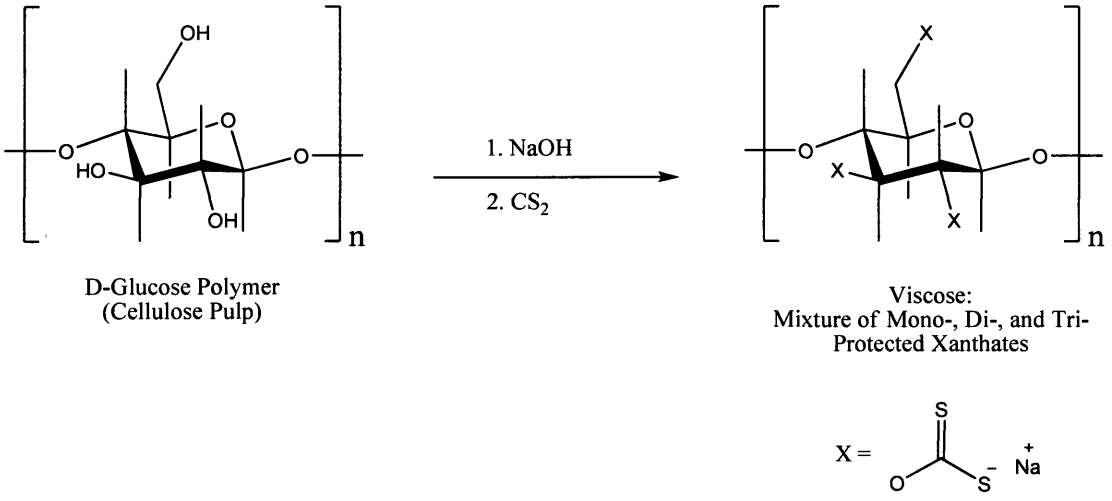
The unique chemical properties of the thiocarbonyl group in turn make the xanthate moiety a distinctive functional group with its own brand of chemistry. As a consequence, the chemistry of xanthates has been an ongoing field of interest that has led to the development and discovery of many interesting and useful chemical applications. Provided below is a brief review of the history and development of xanthate chemistry.

Xanthates in the Industrial Synthesis of Rayon

The notion that the xanthate moiety may be a potentially useful protecting group is largely attributable to the work of polymer chemists and their ongoing efforts to study and understand the

Viscose process. The Viscose process, one of the earliest applications for xanthates, was developed in 1892 by Cross and Bevan as a method to produce "Synthetic Silk".[10] This method is still used today in the production of Rayon and Cellophane and has remained essentially unchanged.[10, 11] The general procedure for Viscose synthesis involves the use of xanthate salts.

Figure 5: The Synthesis of Viscose[10,11]



D-Glucose Polymer
(Cellulose Pulp)

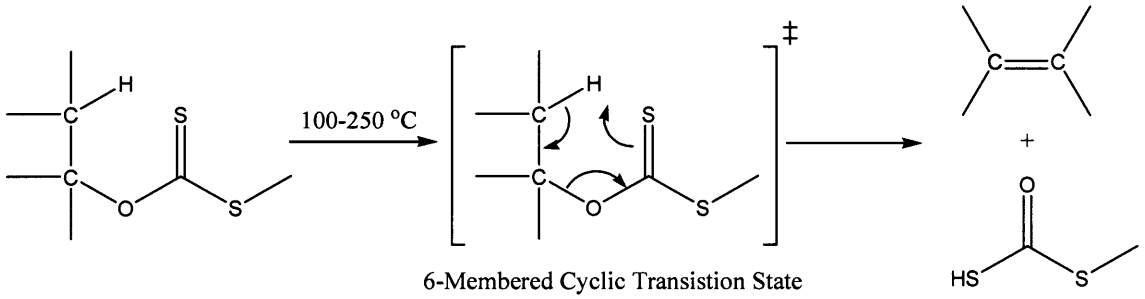
Viscose:
Mixture of Mono-, Di-, and Tri-
Protected Xanthates

In this process, the D-glucose polymer, Cellulose, is collected as the primary component of wood pulp. After shredding and mildly processing the cellulose polymer, it is treated with caustic soda (NaOH) to deprotonate the hydroxyl groups. The electrophile, carbon disulfide, is then added to produce polymer chains of mono, di and tri-xanthate protected monomers, which takes the form of a yellow viscous liquid (Viscose). This liquid is aged, filtered, and later threaded out of a small hole into a bath of sulfuric acid. As the Viscose is drawn from the hole, the xanthates are removed and the cellulose polymers recystallize via hydrogen bonding into a single cohesive fiber.[10] It should be noted that, though it was unknown at the time, the work of Cross and Bevan was one of the first documented cases of both the protection and deprotection of an alcohol involving the xanthate functionality.

Chugaev Elimination

In 1899 L. A. Chugaev reported that xanthates, when heated, undergo a thermal elimination reaction.[12,13] This reaction, the Chugaev elimination, is an important reaction because it enables chemists to add points of unsaturation to xanthate protected alcohols in both a controlled and predictable manner.[14] In contrast, the conventional alcohol elimination reaction known as acid catalyzed dehydration is difficult to predict or control because rearrangements are common in the carbocation intermediate.[15] The high level of control over product formation in the Chugaev elimination is a direct result of the mechanism shown below in Figure 6.[16]

Figure 6: Chugaev Elimination Mechanism[16]

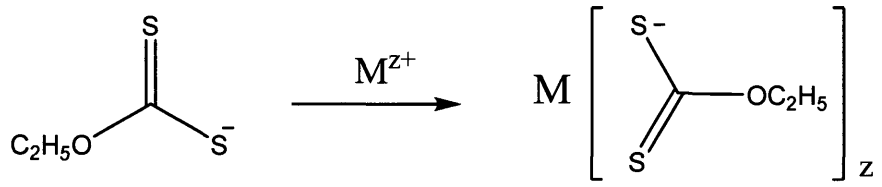


This elimination mechanism includes a concerted 6-membered cyclic transition state which is initiated by the sulfur of the thiocarbonyl as it acts to abstract the beta-hydrogen.[14] Synthetically, this reaction has been instrumental for the synthesis of alkenes from particularly rearrangement-sensitive alcohols.[17]

Xanthates in Mineral Processing

Since 1925, xanthate salts have been an extremely important and useful tool in the flotation methods that are employed in the processing and collecting of non-ferrous metals.[18,19] During this process ore is finely ground and dissolved into an aqueous solution, to which xanthate salts are added. These salts absorb on to the surface of specific minerals making hydrophobic sulfide-mineral complexes, which can be effectively separated.[20]

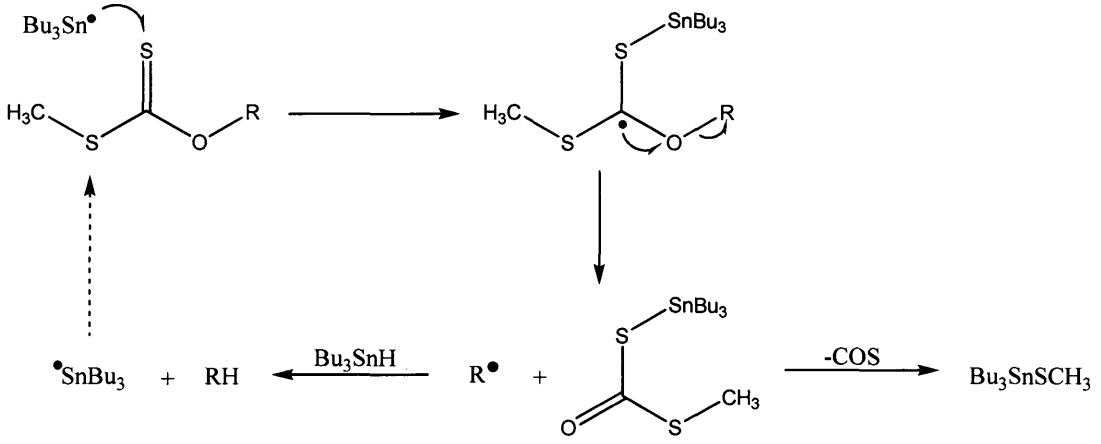
Figure 7: Selective Absorption of Minerals



Barton McCombie (radical reaction)

A very important synthetic application for xanthates came in 1975, when Barton and McCombie reported a method for deoxygenating secondary alcohols by reacting the corresponding xanthates with tributylsilane in a radical reaction (Figure 8).[21]

Figure 8: The Barton-McCombie Mechanism[22]

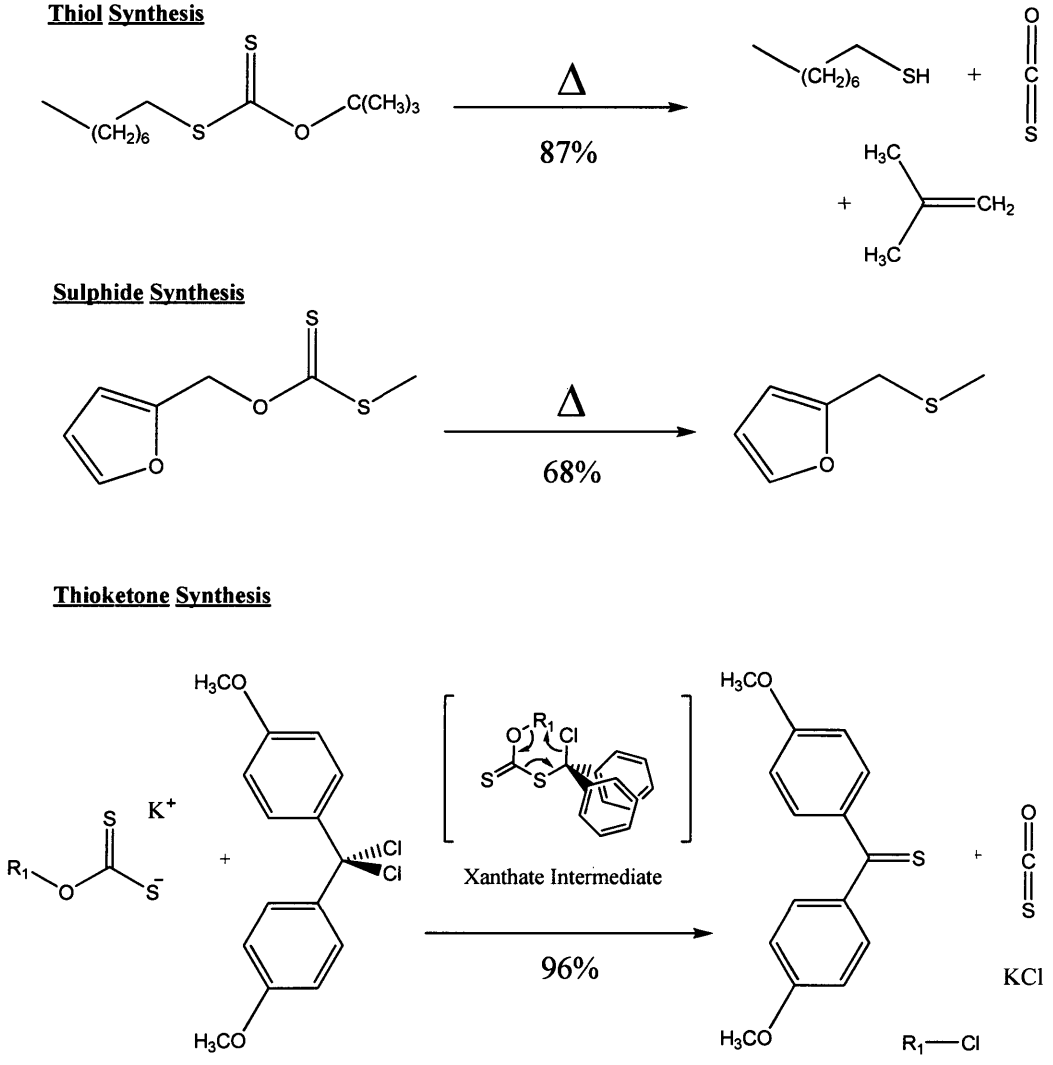


It should also be noted that the mechanism not only deoxygenates the original alcohol but it also produces a carbon radical in the process. This is especially useful because it allows for an efficient method for producing carbon radicals from alcohols.[21] Later studies by Crich and Quintero, have shown that these carbon radicals can also be used as a method to form carbon-carbon bonds.[23]

Xanthates as a Precursor to Other Sulfur Containing Compounds

The xanthate functionality has also shown to be very useful as a precursor to other sulfur containing compounds such as thiols,[24, 25, 26] sulfides,[27, 28] and thioketones.[29] Examples of such reactions are presented below in Figure 9.

Figure 9: Synthesis of Thiols[26] Sulfides[27] and Thioketones[29]



Traditional synthesis of sulfur-containing compounds often relies on the use of hydrogen sulfide, which is both hazardous and difficult to handle.[15] These reactions demonstrate well the importance of xanthates in providing an alternatively safe and effective synthetic route.

Xanthates as Protecting Groups

It is a common procedure in multi-step syntheses to mask hydroxyl groups through protective measures.[1] This technique is especially useful as a means to temporarily obscure the acidic hydrogen so that other reactions (hydroxyl sensitive) can modify the substrate undeterred. At a later point in the synthesis, the protective group can then be selectively removed to restore the original hydroxyl group, or it can be transformed into a different functionality for alternative uses.

As protective groups, xanthate esters have been generally ignored in the literature.[30] This fact could be due to the fact that scientists have largely focused on the more widely accepted industrial uses, overlooking much of the synthetic potential.[19] Ironically, a careful review of the literature indicates that many studies into the industrial applications of xanthates also provide a solid basis in the argument for xanthates as useful protecting groups.[31] Moreover, the past few decades there have seen many discoveries in xanthate chemistry that are also synthetically relevant in protective applications.[32]

In order to absolutely assess the practicality of the xanthate protective group a complete and thorough review of the literature was carried out to locate all publications germane to this study. Provided in Chapter 2 is an analysis of those publications as well as a comprehensive breakdown of xanthate protective chemistry.

[1] Carey, F. and Sundberg, R. **Advanced Organic Chemistry** 4th Ed. Springer, New York, 2000

[2] Wuts, P. G. M. and Green, T. W. **Greene's Protective Groups in Organic Chemistry.** 4th Ed. John Wiley and Sons Inc., 2007

[3] Fikse, Megan A.; Bylund, William E.; Holubowitch, Nicolas E.; Abelt, Christopher J. **Synthesis of chlorothioformates from xanthates.** Synthesis (2006), (24), 4118-4120.

[4] Dawid, Malgorzata; Mloston, Grzegorz; Warkentin, John. **Relative reactivities of carbonyl and thiocarbonyl groups toward dimethoxycarbene: two new dimethoxythiiranes.** Chemistry--A European Journal (2002), 8(9), 2184-2187.

[5] Campodonico, Paola R.; Fuentealba, Patricio; Castro, Enrique A.; Santos, Jose G.; Contreras, Renato. **Relationships between the Electrophilicity Index and Experimental Rate Coefficients for the Aminolysis of Thiolcarbonates and Dithiocarbonates.** Journal of Organic Chemistry (2005), 70(5), 1754-1760.

[6] Gade, Alexandra M.; Abelt, Christopher J. **S-alkyl chlorothioformates from xanthates.** Synthesis (2007), (14), 2097-2099.

[7] Fichtner, Michael W.; Haley, Neil F. **Trifluoroacetic - acid - catalyzed rearrangement of dialkyl xanthates to dithiocarbonates with inversion of configuration.** Journal of Organic Chemistry (1981), 46(15), 3141-3.

[8] Degani, Iacopo; Fochi, Rita; Regondi, Valeria. **Rearrangement of O , S - dialkyl dithiocarbonates to S , S - dialkyl dithiocarbonates catalyzed by tricaprylmethylammonium chloride.** Synthesis (1981), (2), 149-51.

[9] Al-Kazimi, H. R.; Tarbell, D. S.; Plant, Derek. **Rearrangement of diaryl thionocarbonates to diaryl thiolcarbonates.** Journal of the American Chemical Society (1955), 77 2479-82.

[10]Avram, Moïs Herban. **The Rayon Industry** 2d ed., New York, D. Van Nostrand Company 1929

[11] Russler, Axel; Lange, Thomas; Potthast, Antje; Rosenau, Thomas; Berger-Nicoletti, Elena; Sixta, Herbert; Kosma, Paul. **A novel method for analysis of xanthate group distribution in viscoses.** Macromolecular Symposia (2005), 223(Cellulose and Cellulose Derivatives), 189-199.

[12] Villemin, Didier; Hachemi, Messaoud. **Potassium fluoride on alumina: a convenient synthesis of O -alkyl methyldithiocarbonates. Pyrolysis of O - benzyl S - methyl dithiocarbonates.** Synthetic Communications (1996), 26(13), 2449-2459.

[13] Benkeser, Robert A.; Hazdra, James J.; Burrous, Merwyn L. **Factors influencing the direction of elimination in ester pyrolyses.** Journal of the American Chemical Society (1959), 81 5374-9.

[14] Alexander, Elliot R.; Mudrak, Anton. **Studies of the Mechanism of Chugaev and acetate thermal decompositions. I. cis - and trans - 2 - Phenylcyclohexanol.** Journal of the American Chemical Society (1950), 72 1810-13.

[15] Solomons, T. W. Graham, **Organic Chemistry.** 3rd Ed., John Wiley & Sons, New York, 1984 pp 235

[16] March, Jerry. **Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.** 3rd Ed., John Wiley and Sons, New York, 1985, pp 906

[17] Fuchter, Matthew J. **Chugaev elimination.** Name Reactions for Functional Group Transformations (2007), 334-34. Publisher: John Wiley & Sons, Inc., Hoboken, N. J

[18] Finkelstein, N. P.; Lovell, V. M.. **Fundamental studies of the flotation process. Work of the National Institute for Metallurgy.** Journal of the South African Institute of Mining & Metallurgy (1972), 72(12), 328-42.

[19] Rao, Ramachandra S. **Xanthates and Xanthate Related Compounds.** Marcel Dekker, Inc., New York. 1971

[20] Silvester, Ewen; Truccolo, David; Hao, Fu Ping. **Kinetics and mechanism of the oxidation of ethyl xanthate and ethyl thiocarbonate by hydrogen peroxide.** Journal of the Chemical Society, Perkin Transactions 2 (2002), (9), 1562-1571.

[21]Barton, Derek H. R.; McCombie, Stuart W.. **New method for the deoxygenation of secondary alcohols.** Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1975), (16),

[22] Zard, Samir Z. **The genesis of the reversible radical addition-fragmentation-transfer of thiocarbonylthio derivatives from the Barton - McCombie deoxygenation: A brief account and some mechanistic observations.** Australian Journal of Chemistry (2006), 59(10), 663-668.

[23] Crich, David; Quintero, Leticia. **Radical chemistry associated with the thiocarbonyl group.** Chemical Reviews (Washington, DC, United States) (1989), 89(7), 1413-32.

[24] Isola, Mauro; Ciuffarin, Ennio; Sagramora, Laura. **A convenient synthesis of optically active thiols.** Synthesis (1976), (5), 326-9.

[25] Fredga, Arne. **Optical antipodes of □ -(ethylcarbonyldithio) phenylacetic acid.** Arkiv. Kemi, Mineral. Geol. (1947), 24B(No. 15), 8 pp.

[26] Degani, Iacopo; Fochi, Rita; Santi, Marco. **The phase - transfer synthesis of alkanethiols from alkyl halides via O-tert-butyl-S- alkyl dithiocarbonates.** Synthesis (1977), (12), 873-4.

[27] Eto, Masashi; Nishimoto, Mituhiro; Uemura, Toshihiro; Hisano, Takuzo; Harano, Kazunobu. **Simple synthesis of furfuryl sulfides via extrusion of COS from the xanthates and its mechanistic aspects.** Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1995), (6), 1155-62.

[28] Degani, Iacopo; Fochi, Rita; Regondi, Valeria. **The phase - transfer synthesis of unsymmetrical dialkyl sulfides via O,S- dialkyl dithiocarbonates.** Synthesis (1979), (3), 178-81.

[29] Schoenberg, Alexander; Frese, Emil. **Organic sulfur compounds. LV. Reactions of gem - dixanthylmethanes and their formation from gem - dichlorides with potassium xanthate.** Chemische Berichte (1968), 101(2), 716-24.

[30] (a) Wuts, P. G. M. and Green, T. W. **Greene's Protective Groups in Organic Chemistry.** 4th Ed. John Wiley and Sons Inc., 2007. p. 297. (b) Sato, S.; Furukawa, N.. **Thiocarbonic acids and derivatives.** Science of Synthesis (2005), 18 821-968. (c) Paquette, L. A. **Encyclopedia of Reagents for Organic Synthesis**. John Wiley and Sons. New York. Vol. 8, 5412-5416

[31] (a) Willard, John J.; Pacsu, Eugene. **Location of xanthate groups in viscose.** Journal of the American Chemical Society (1960), 82 4350-2. (b) Willard, John J.; Pacsu, Eugene. **New method of removing xanthate groups from carbohydrates. Chemical structure of methyl □ -D-glucopyranoside monoxanthate.** Journal of the American Chemical Society (1960), 82 4347-50. (c) Adamek, E. G.; Purves, C. B. **The location of xanthate groups in partially substituted starch xanthates.** Canadian Journal of Chemistry (1960), 38 2425-32. (d) Reference 11

[32] See Chapter 2

Chapter 2

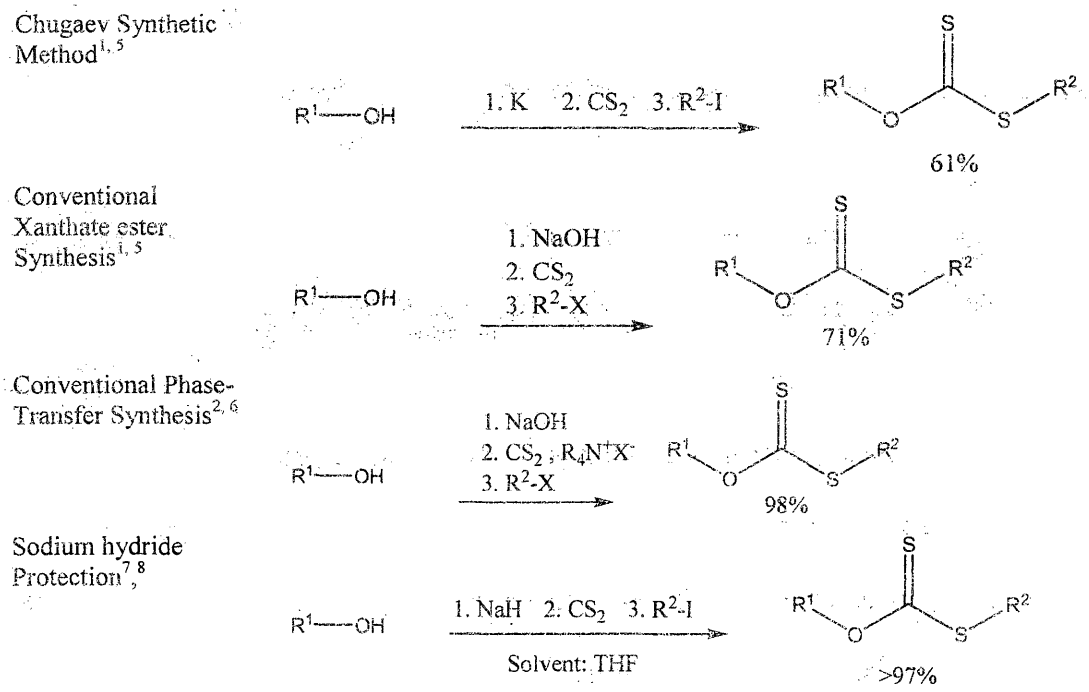
The Protective Chemistry of Xanthate Esters

Protective Procedures

Until recently, it was difficult to make a compelling case for xanthates as versatile protective groups because conventional synthesis methods utilize strongly basic or alternatively reactive conditions in order to create the initial alkoxide intermediate.[1, 2, 3] This factor is a challenge because such extreme environments are not necessarily conducive to other functionalities and/or protecting groups.

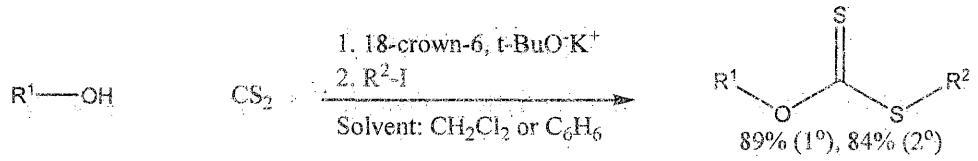
For example, the original Chugaev method for xanthate ester synthesis involved the use of metallic potassium which was extremely inconvenient and dangerous.[1] Another method for synthesis involves the commonly used base, hydroxide, which is particularly problematic. Not only is the hydroxide ion a strong base, but it is also a substantial nucleophile, capable of hydrolyzing numerous functionalities.[1, 4] To avoid the use of hydroxide chemists have used sodium hydride as a base, and although this method gives exceptionally high yields, the hydride anion is still extremely basic.[3] These early synthesis procedures are generally ineffective as protective methods because they necessitate harsh and reactive conditions that may compromise complex substrates with other functionalities.

Figure 1: Early Synthesis Methods



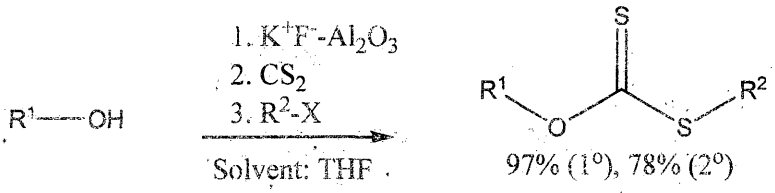
Chemists have developed other less extreme synthesis methods that may prove useful. For example, the issue of nucleophilic hydroxides can be easily overcome with the use of bulky bases that are too sterically hindered to act as effective nucleophiles. This method is described in a study by Chenevert and co-workers in which potassium *tert*-butoxide was used as a base to successfully prepare xanthate esters in good yields.[9] However, potassium *tert*-butoxide is still a strong base, which may pose problems. It should also be noted that the size of the base can be a limitation when the target hydroxyl group is positioned within a highly substituted substrate.

Figure 2: Xanthate Protection via Bulky Base[9]



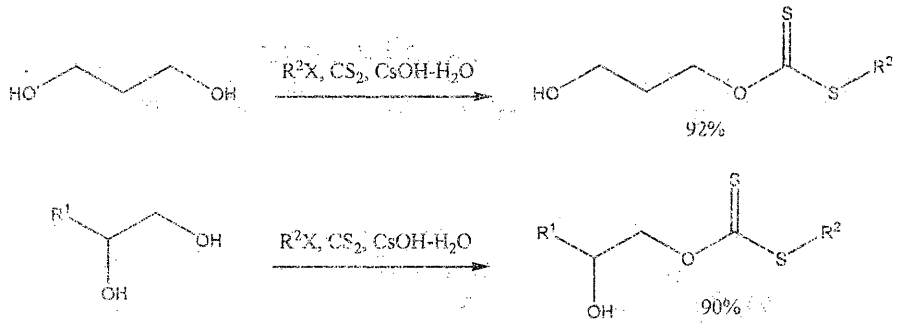
Another way to deal with the challenge is to develop a protection method that uses extremely mild basic conditions. One such method was developed by Villemin and Hachemi.[10] Their procedure involves treating a solution of alcohol and THF with potassium fluoride on alumina to form the desired alcoholate.

Figure 3: **Villemin- Hachemi Xanthate Protection[10]**



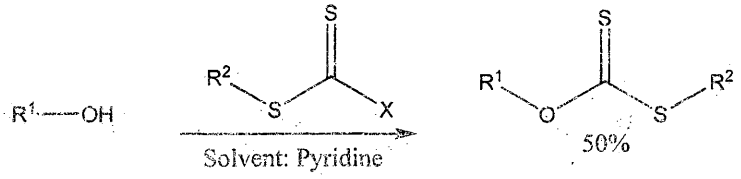
Recently, Nagle and Coworkers discovered a synthetic method that allows chemists to selectively add one xanthate to substrates with more than one hydroxyl group.[11] Their work demonstrates that both symmetric and asymmetric diols can be mono-protected to give high selectivity and good yields. It was also shown that similarly exceptional selective protection of 1° hydroxyl groups can be obtained while unprotected 2° alcohols are on the same substrate, in close proximity.

Figure 4: Selective Mono-protection[11]



One final and particularly promising protection method, studied in our lab, involves a simple one-step protective reaction.

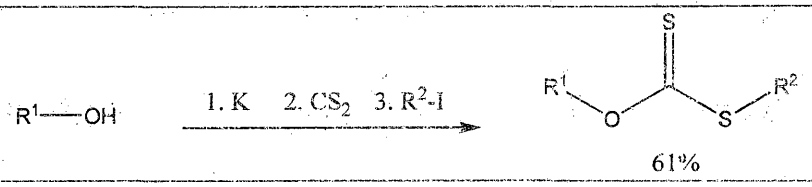
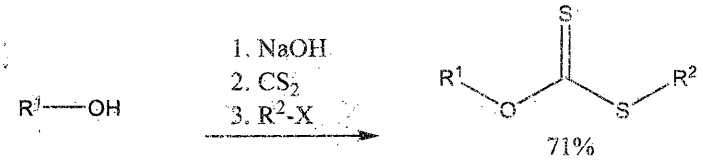
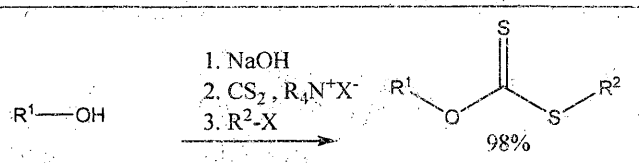
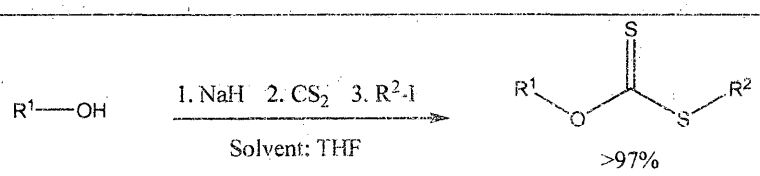
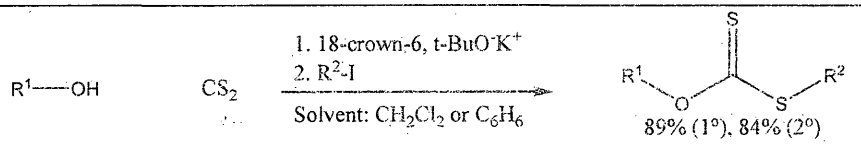
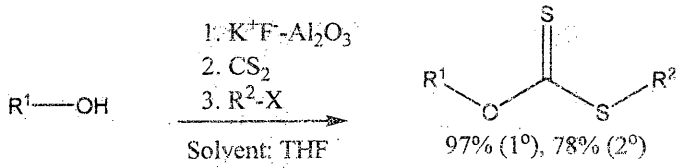
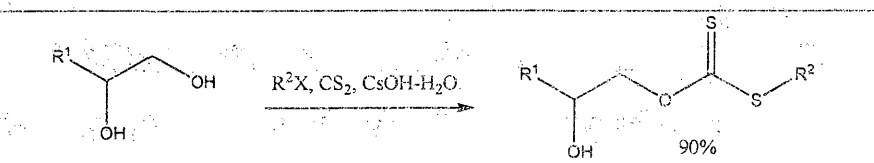
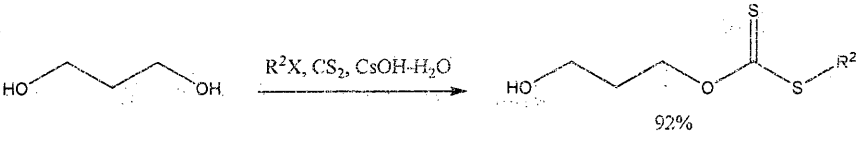
Figure 5: Protective Acylation[12,13]

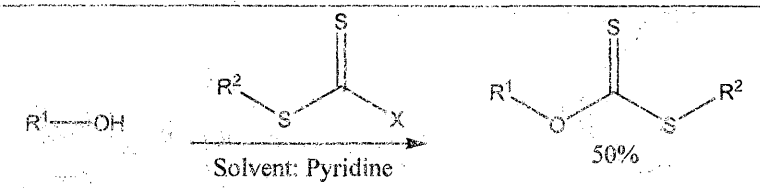


This is accomplished via an acylation reaction between the alcohol and an alkyl halodithioformate. The methods and procedures for this reaction are discussed in Chapter 5.

It is evident from the methods discussed and presented above that xanthate protection is achievable through a variety of methods and conditions. The next step in evaluating the xanthate protective group is to discuss the chemistry of the xanthate ester as well as the reaction conditions which have been verified as xanthate-stable. Provided below in Table 1 is a collection of the various xanthate protective reactions.

Table 1: Protective Reactions

Chugaev Synthetic Method [1,5] (Hygroscopic and Dangerous)	
Conventional Xanthate ester Synthesis [1, 5] (Strongly Basic)	
Conventional Phase-Transfer Synthesis [2, 6] (Strongly Basic)	
Sodium hydride Protection [7, 8] (Strongly Basic)	
Xanthate Protection via Bulky Base [9] (Strongly Basic, Non-Nucleophillic)	
Villemin- Hachemi Xanthate Protection [10] (Very Mildly Basic)	
Selective Mono-protection [11] (Strongly Basic)	 

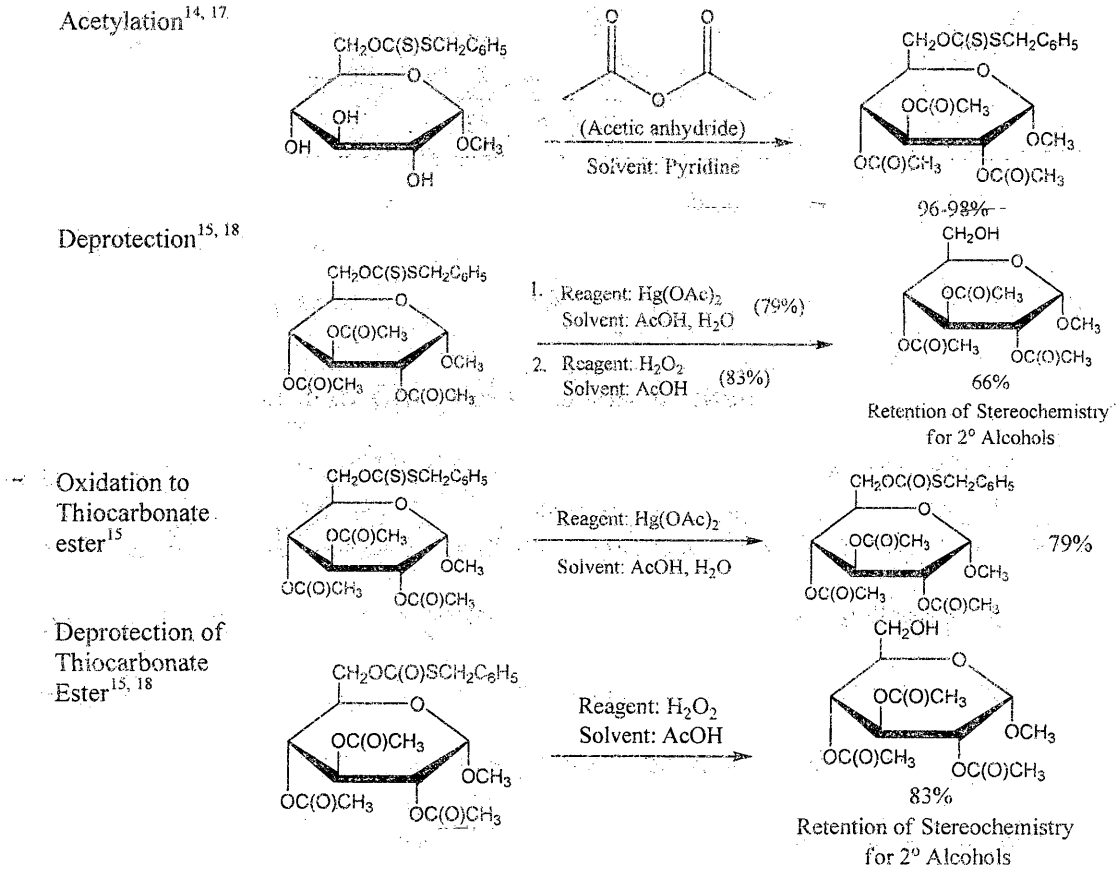
Protective Acylation [12, 13] (Neutral)	

The Xanthate Ester Group in Viscose Studies

For over half a century there have been numerous published studies describing various attempts to determine the specific substitution pattern of sodium xanthate in Viscose.[14, 15, 16] This topic of study is important because both the degree and consistency of xanthate substitution has a direct influence over the resulting properties of the polymer product.[16] Conveniently, some of these studies have incorporated protective group methods which necessitate the stabilization of the sodium xanthate moiety to the xanthate ester.

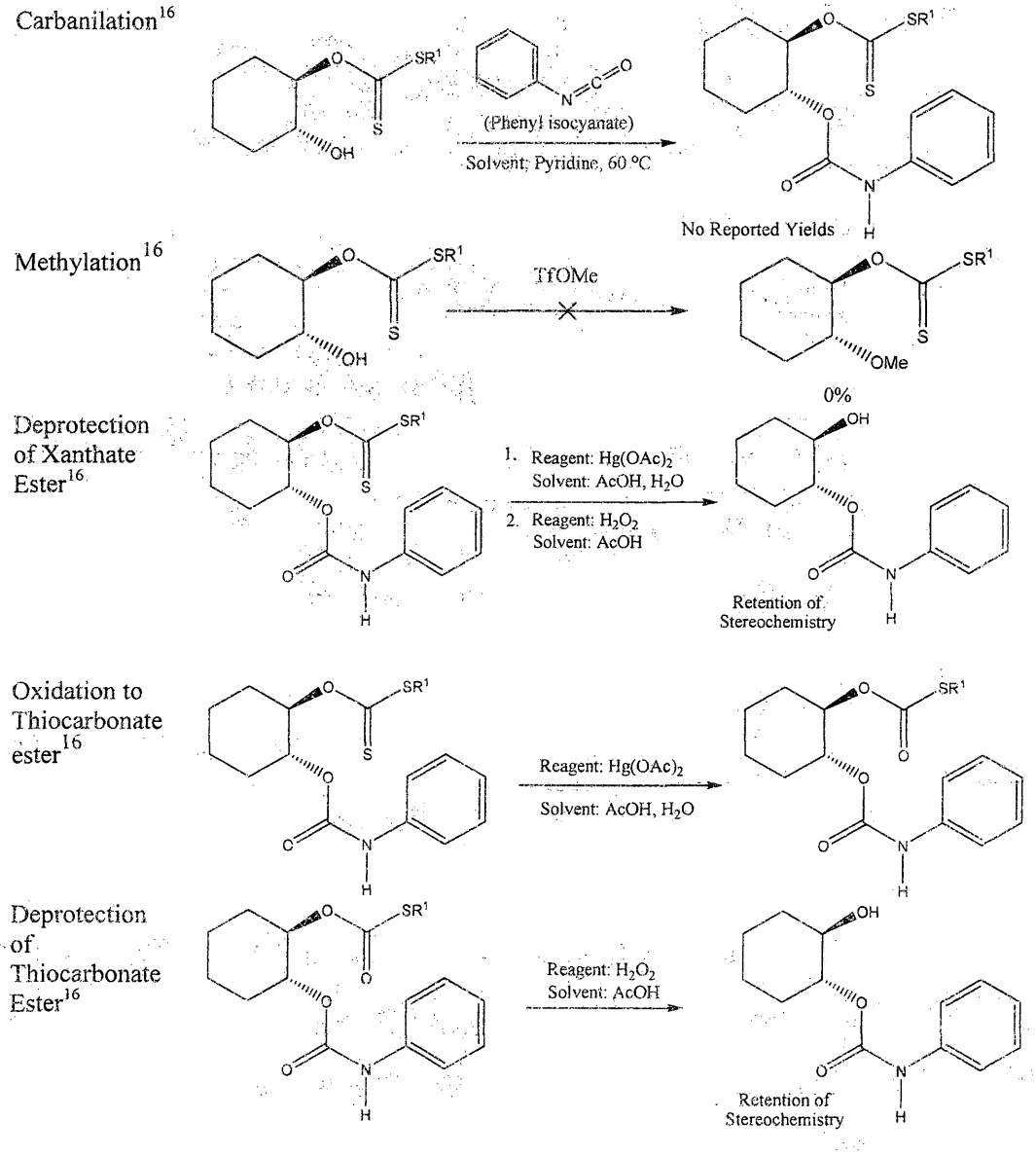
In 1960, Willard and Pascu published several papers that involved the study of xanthate esters in Viscose.[14, 15] In these studies they reported that for substrates with both xanthate protected alcohols and free hydroxyl goups, the xanthate moiety was conserved during acetylation (Esterification with Acetate) of the free hydroxyl groups. Additionally Willard and Pascu discovered a mild two-step procedure for the removal of the xanthate ester. This method involves the conversion of the xanthate ester into its corresponding O,S-dialkyl-thiocarbonate by way of mercuric acetate, which is then followed by oxidation via hydrogen peroxide in glacial acetic acid to regenerate the original alcohol with retention of stereochemistry.[15] This deprotection method was also shown to be nonreactive for acetylated groups.

Figure 6: Willard and Pascu Viscose Reactions



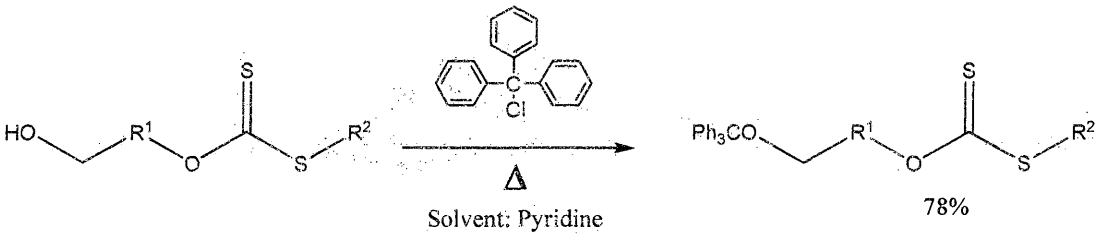
In a later study, Kosma and co-workers demonstrated that free hydroxyl groups in partially xanthate protected Cellulose can undergo carbanilation (the addition of phenyl-isocyanate) while conserving the xanthate ester groups.[16] These investigators also reported that the xanthate removal procedure proposed by Willard and Pascu did not affect the carbanilated groups, which is synthetically useful. Additionally, xanthate-protected substrates were shown to be unstable in methylation conditions using methyl triflate due to the nucleophilic nature of the thiocarbonyl. It is likely that other highly sensitive electrophiles are similarly vulnerable to the mildly nucleophilic sulfur of the thiocarbonyl.

Figure 7: Kosma Studies of Viscose and Cellulose



Tritylation was also shown by Adamek and Purves to be effective with partially protected sugars.[19] Their work indicates that tritylation of primary alcohols in xanthate containing substrates is accomplished in good yields by the use of excess trityl chloride in pyridine with heat. The group also carried out extensive studies in the process of dexanthation. However, only one method proved effective and it was limited to extremely small scales due to the inherent risk of explosion when working with chlorine dioxide.

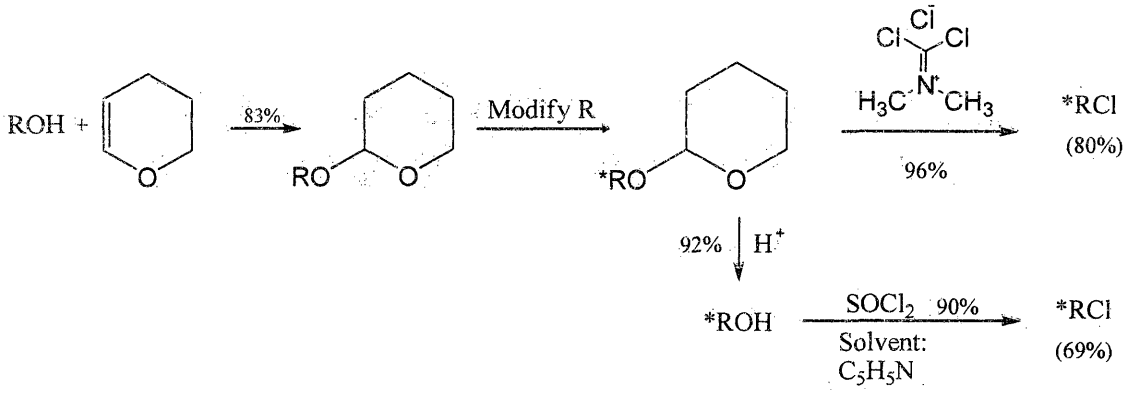
Figure 8: Tritylation [19,20]



Transformation Reactions

The addition and removal of protective groups suggests that they play a primarily passive role in synthesis reactions.[21] Moreover, because the process is never 100% efficient, there is ultimately some loss of the final product. However, if the eventual fate of a protected functional group is removal or conversion, then the direct transformation of the group, in its protected state, is a useful and effective method to condense multiple steps of a reaction sequence.[22] Below, in Figure 9, is an example comparing the direct chlorination of a THP-protected hydroxyl to the less efficient approach of deprotection before chlorination.

Figure 9: Chlorination of THP-protected Alcohol[23]



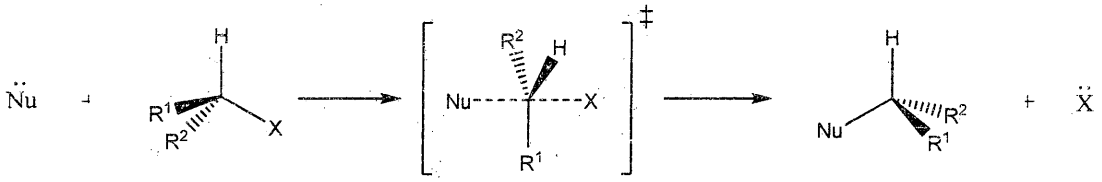
Treating an alcohol to form the corresponding xanthate ester is not only a protective measure, but it is also an effective way to convert the hydroxyl moiety into a

favorable leaving group.[24] Furthermore, as seen in Chapter 1, the unique reactivity of xanthates can also be utilized in a controlled manner to prepare a variety of different functionalies. Provided below are the transformative reactions of the xanthate protective group.

Heterolytic Transformations of Xanthate Protected Alcohols

The direct conversion of a protected alcohol to the corresponding alkyl halide has been shown to be an important and useful synthetic step in organic chemistry.[25, 26, 27] These reactions are typically heterolytic (S_N2) displacement reactions (Figure 10), and involve a nucleophilic attack of the hydroxyl-carbon by a halide anion (Nu), coupled with the displacement of the protected-hydroxyl moiety (X). For 1° Alcohols (R^1=alkyl, R^2=H) stereochemistry is not a factor, but for chiral 2° Alcohols (R^1=alkyl, R^2=alkyl) there is inversion of product stereochemistry. Synthetically these reactions can be very useful because the chirality, though inverted, is still preserved.

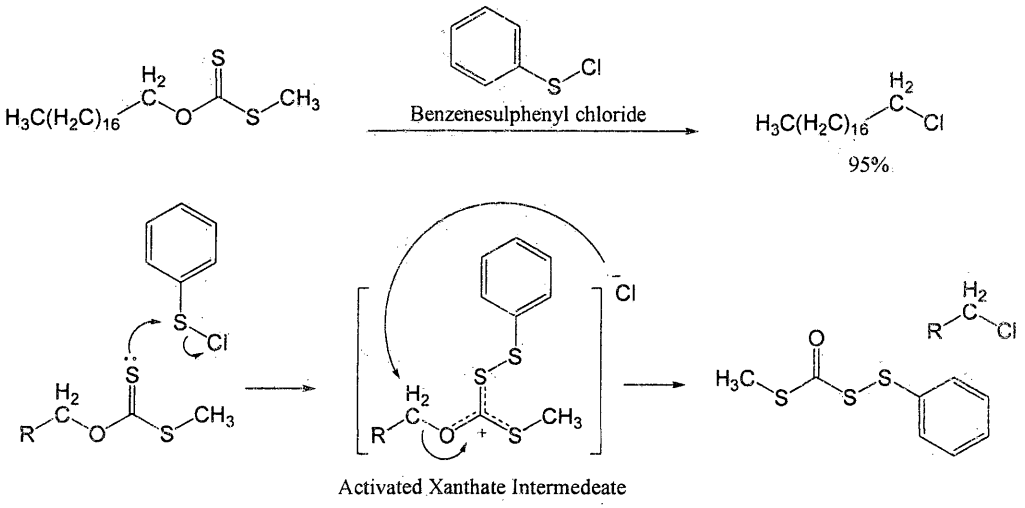
Figure 10: General S_N2 Displacement Reaction



The xanthate protective group has particularly unique reactive properties for heterolytic reactions. This is because the xanthate moiety by itself is not quite sufficient as a ready leaving group, but can be readily removed given the appropriate conditions. Barton and co-workers demonstrated this well by utilizing a variety soft (mild) electrophiles to both activate the xanthate group while simultaneously producing a nucleophilic halide anion.[24] Their results provide excellent results for chlorination

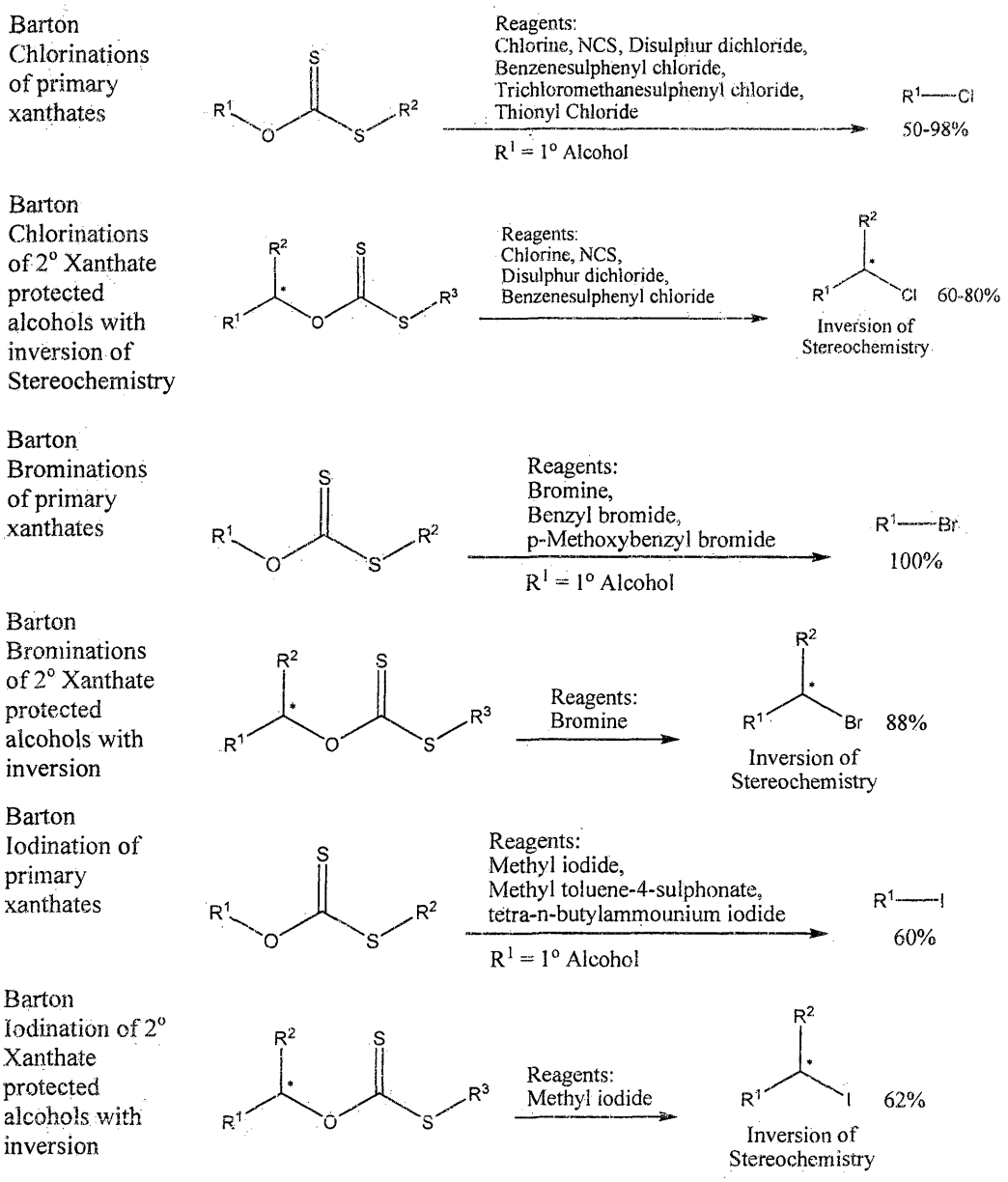
reactions, as well as a few cases for bromination and iodination. Provided below is one of the xanthate displacement reactions for the soft electrophile benzenesulphenyl chloride with a xanthate-protected 1^{o} alcohol.

Figure 11: Chlorination of 1^{o} Xanthate-protected Alcohol [24]



As discussed above, the nucleophilic thiocarbonyl sulfur attacks the electrophile reagent to displace the chloride anion. The subsequent intermediate contains a highly destabilized leaving group (activated xanthate) which is then easily displaced by the chloride anion. The group was also able to show that certain electrophiles react similarly with chiral 2^{o} alcohols to give the chloro-, bromo-, and iodo-products in high yields with inversion of stereochemistry. The complete list of reactions and reagents is listed in Figure 12 below.

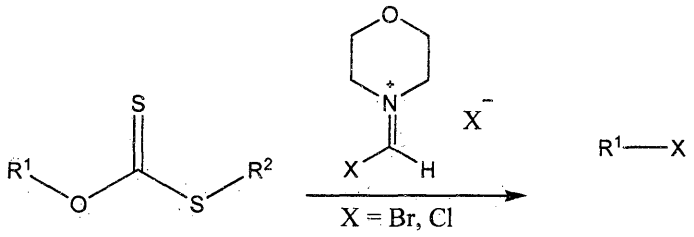
Figure 12: Barton Halogenation Reactions by way of Soft Electrophiles [24]



Another soft electrophile, the Vilsmeier reagent, has been studied extensively in our lab and shown to give similar results to those of the Barton group for the chlorination and bromination reactions.[28] The use of the Vilsmeier reagent in these reactions is

particularly promising because the chlorine, bromine derivatives are relatively simple to prepare and serve as sufficiently mild electrophiles for attack by the thiocarbonyl.[28]

Figure 13: Vilsmeier Reagent Halogenation of Xanthate-Protected Alcohols



A complete discussion of the Vilsmeir reagent and the experimental details of our study is provided in Chapter 4.

When working with heterolytic S_N2 displacements, however, there are limitations. Sterics and/or geometry can effectively inhibit the nucleophile from interacting at all with the intended substrate. Moreover, the S_N2 displacement could be in competition with an S_N1 reaction, where the substrate decomposes into a planar carbocation intermediate resulting in a racemic product. There are also instances in which proximal hydrides or alkyl groups can easily rearrange to accommodate the S_N1 mechanism.[29,30] Such reactivity can result in multiple halide products with little or no specificity as well as undesired rearrangements in the carbon backbone of the substrate.[31] Modifying reaction conditions such as solvent polarity and temperature is one way to avoid competition reactions.

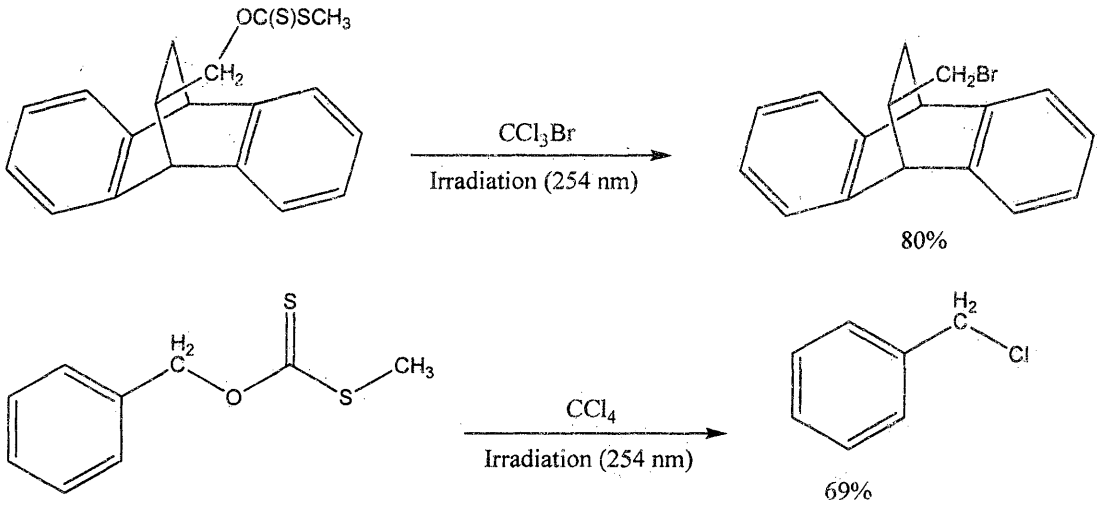
Homolytic Transformations of Xanthate Protected Alcohols

Another potential solution to these challenges involves the use of homolytic pathways to control product outcome.[31] An excellent example of homolytic transformations can be found in the work of Jenson and Moder. They demonstrated in

their research that an alcohol can be modified with a unique protective group (in their case t-butylperoxyglyoxalates) that in turn can be selectively treated to homolytically decompose to the corresponding alkyl halide. The reaction is particularly useful because it produces products in high yields and free of rearrangements.[31] Moreover, because these reactions do not involve an attack at the hydroxyl carbon, the effect of sterics and geometric constraints is greatly diminished.

The xanthate ester functionality has also been reported in the literature as a reasonably useful group for homolytic transforms to form a number of different functionalities.[27, 32, 33, 34] In 1982, Cristol and Seapy preformed an exploratory study on radical-initiated transformations of xanthate-protected alcohols to their corresponding chloride and bromide derivatives. Though they ultimately determined their methods to be impractical as a generally applicable synthetic procedure, they were able to show a few interesting examples in which photolysis of certain xanthate groups gives the corresponding alkyl halide in yields as high as 80%.[27] above Furthermore, their reaction proved to be extremely useful for the bromination of some substrates that express a high level of unreactive character toward the more conventional S_N1 and S_N2 reactions.

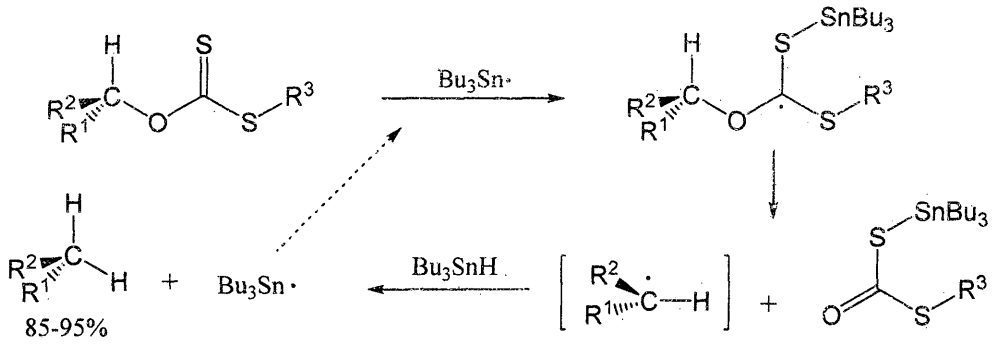
Figure 14: Photolysis of Xanthate Esters to give Alkyl Halides [27]



This radical method, however, does not conserve stereochemistry due to the planar radical intermediate formed just after ejection of the xanthate group (see Figure 15).

The Barton reduction reaction is a similar and very commonly utilized radical reaction. In 1981, Barton and Motherwell reported that xanthate-protected secondary alochols can be reduced (deoxygenated) by trialkyl tin hydrides.[32]

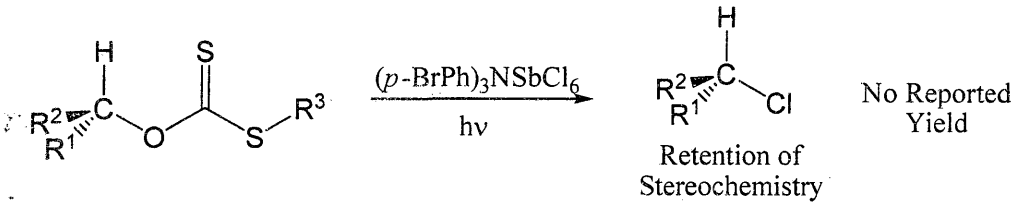
Figure 15: Barton Reduction of Xanthate Protected Alcohols [32]



This method of deoxygenation has proven to be extremely useful in multi-step syntheses.[35] Additionally, similar reduction schemes have also been developed by Ballestri and co-workers which utilize *tris*(trimethylsilyl)silane as the radical initiator.[36]

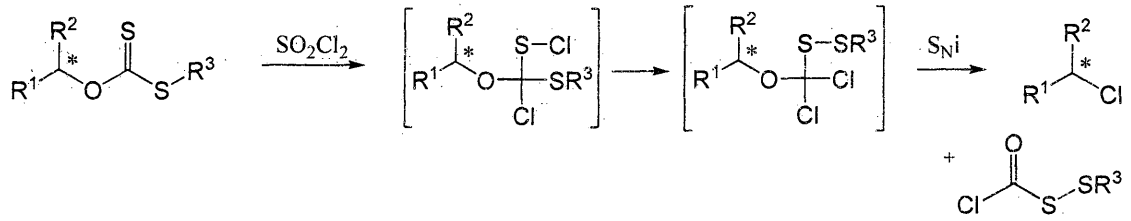
One homolytic radical reaction that has demonstrated conservation of stereochemistry in the transformation of xanthates, is the photoinduced plectron transfer (PET) reaction.[34] In 1992, Barton and co-workers reported that xanthate protected hydroxyl groups can be converted to the corresponding chlorides with retention of stereochemistry via irradiation in the presence of *tris*(4-bromophenyl)ammonium hexachloroantimonate. The mechanism of this reaction was not explained in detail, but it is believed to produce a radical intermediate on the xanthate group that reacts with chloride to decompose in a manner allowing for retention.

Figure 16: PET Reaction [34]



Though Jenson and Moder focused specifically on radical chemistry, the idea of a homolytic reaction is applicable to non-radical mechanisms as well. A great advantage to using a non-radical procedure is that scrambling of stereochemistry may be completely avoided by eliminating the planar radical intermediate. Currently, one such method exists that is commonly used to transform xanthate-protected alcohols to the corresponding chloride derivative. This approach, reported by Kozikowski and Lee, involves treating the xanthate moiety with SO_2Cl_2 to give the chlorine derivative in high yields with retention of stereochemistry.

Figure 17: Chlorination of 2° Xanthate-Protected Alcohols with Retention of Configuration [33]

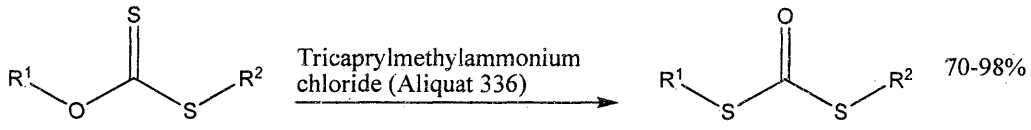


Here the reagent initially reacts with the xanthate substituent to form an intermediate which rearranges into a second intermediate and then finally collapses in an internal S_Ni type mechanism to form the chlorinated product.[21, 33] This reaction is extremely useful for 2° and sterically hindered alcohols.[21] Presently, there are no published analogous reactions for the bromination or iodination of sterically hindered 2° alcohols.

Transformations of the Xanthate Ester Group into Other Functional Groups

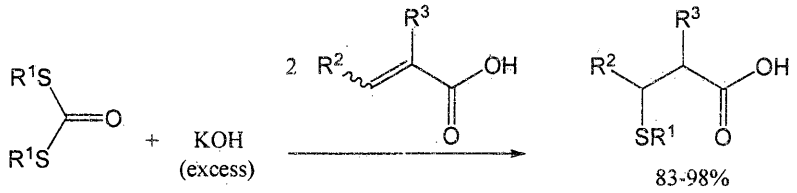
Another useful application for the xanthate group is its ability to serve as a precursor to other protective and/or reactive functionalities. As first discussed in chapter 1, the xanthate ester group is known to rearrange to the form the more stable *S,S*-dialkyl-dithiocarbonates.[37]

Figure 18: Rearrangement of Xanthate Esters to *S,S*-Dialkyl-dithiocarbonates[38]



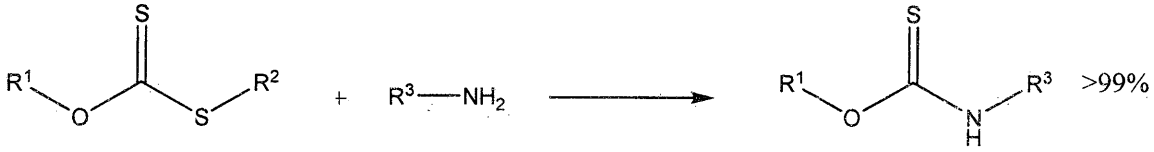
This reaction is particularly useful because *S,S*-dialkyl-dithiocarbonates can undergo hydrolysis in aqueous potassium hydroxide to give the alkane thiolate derivative of the original alcohol.[39] Moreover, the thiolate anion can be immediately consumed as a nucleophile in the same reaction pot to give alkylthiocarboxylic acids in good yields.[40]

Figure 19: Hydrolysis of S,S-Dialkyl-dithiocarbonates[40]



Another useful transformative reaction for xanthate protected alcohols is the conversion of a xanthate ester to a thiocarbamate.

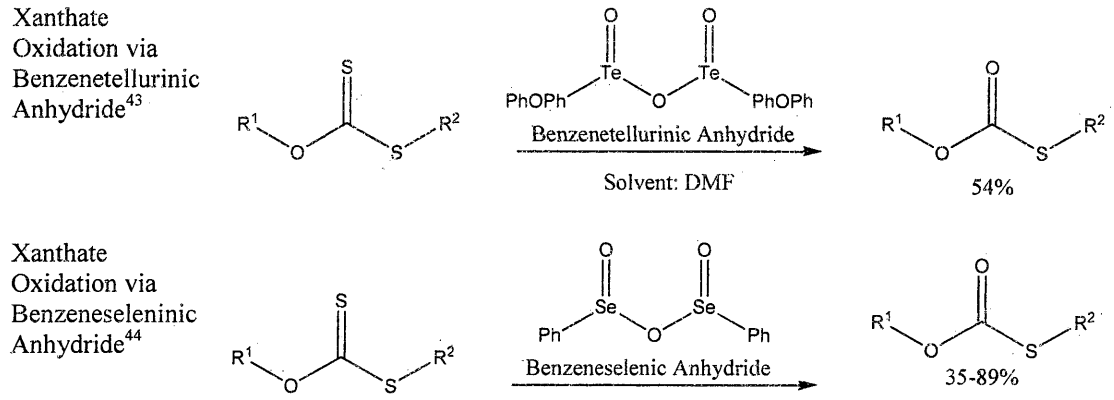
Figure 20: Xanthate Transformation to Thiocarbamates[41]



This reaction is easily preformed under mild conditions and is noteworthy because the Thiocarbamate moiety has also been studied and confirmed to be a useful protective group for alcohols.[22, 42] Earlier work in our lab has also demonstrated that the thiocarbamate group reacts well with the Vilsmeier reagent to give the alkyl bromide derivative of the original alcohol in good yields.[22]

Previously, in the discussion of xanthates in Viscose studies, *O,S*-dialkylthiocarbonates appeared as the oxidized intermediate formed during the first step of the Willard and Pascu xanthate deprotection procedure. Besides the mercuric acetate oxidation, benzenetellurinic anhydrides and benzeneselenic anhydrides have also been reported in the literature as suitable oxidizing agents for the transformation of xanthates to *O,S*-Dialkylthiocarbonates.

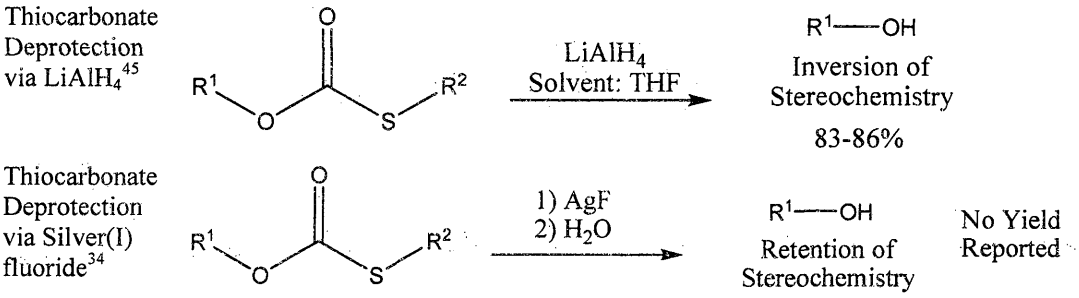
Figure 21: Alternative Xanthate Oxidation Reactions



Though these oxidants give lower yields, they are useful alternatives for when reaction conditions are not conducive to the Willard and Pascu protocol.

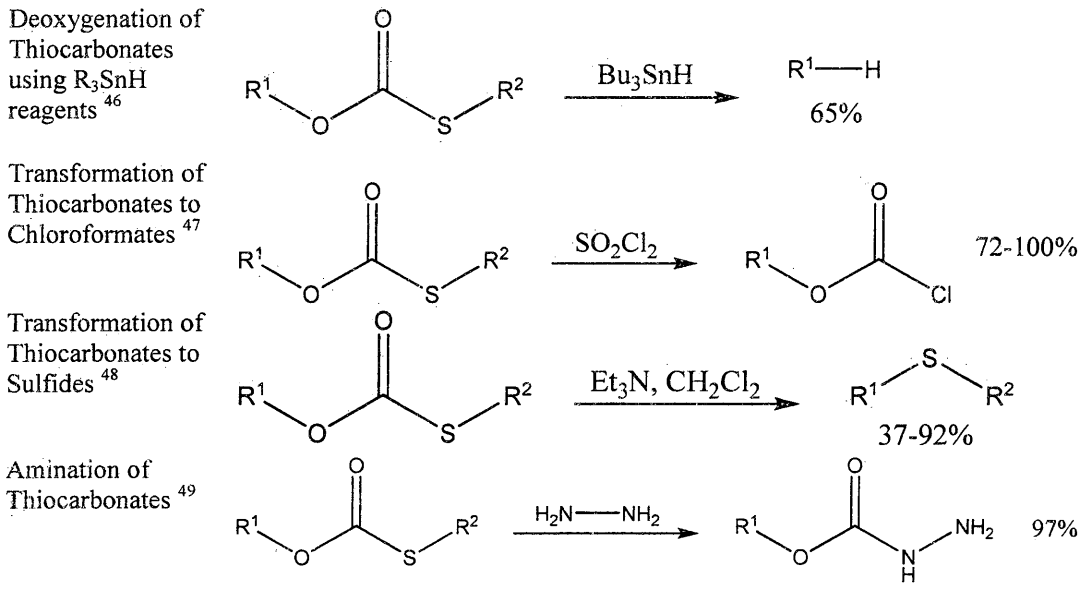
O,S-dialkyl-thiocarbonates are also a very versatile functional group. Willard and Pascu reported, as previously discussed, that the thiocarbonate group can be removed to give the original alcohol with retention of stereochemisty. There are also other deprotection methods that reproduce the alcohol with controlled stereochemistry, thus providing multiple pathways by which retention or inversion may be obtained.

Figure 22: Alternative Thiocarbonate Deprotection Methods



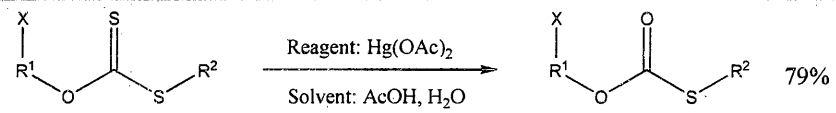
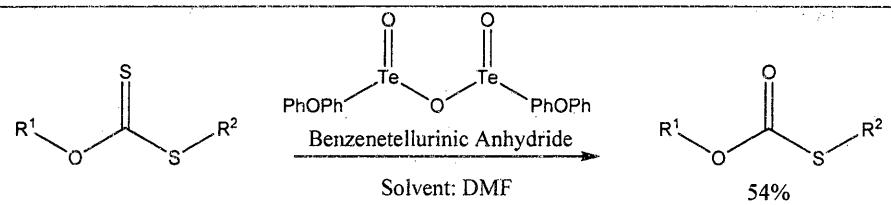
O,S-dialkylthiocarbonates are also able to react to form a wealth of other potentially useful substrates. A list of reactions is provided below in figure 23.

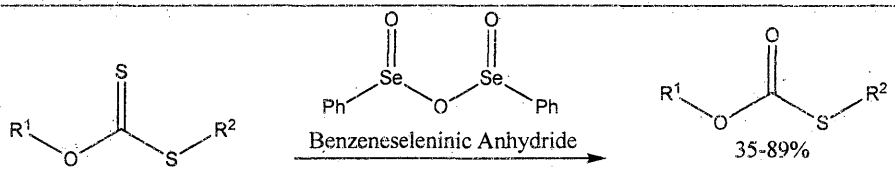
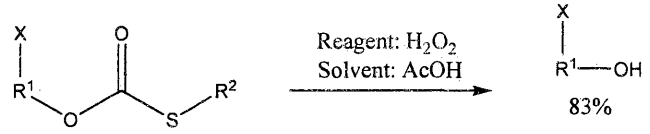
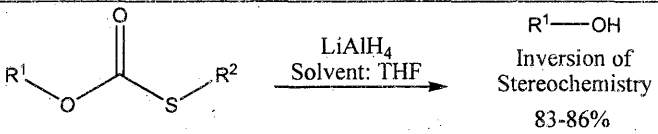
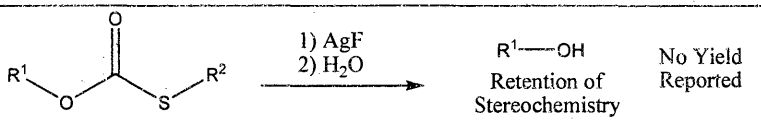
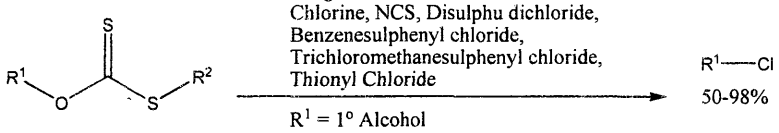
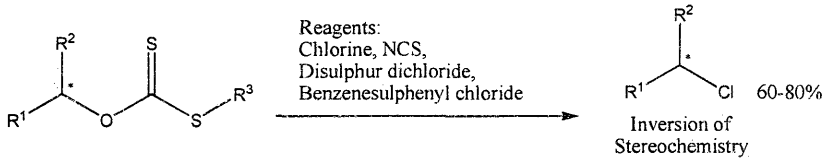
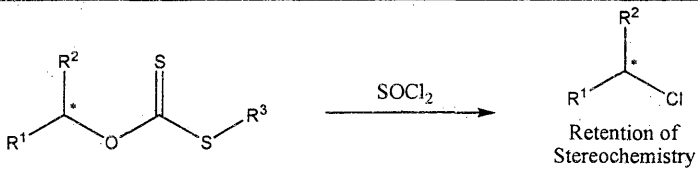
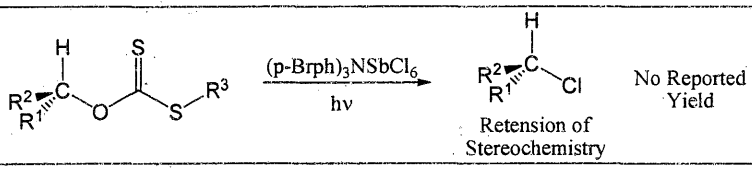
Figure 23: Transformation Reactions of Thiocarbonates

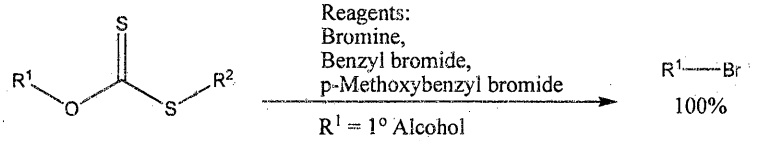
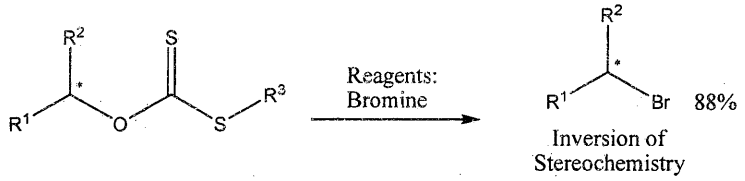
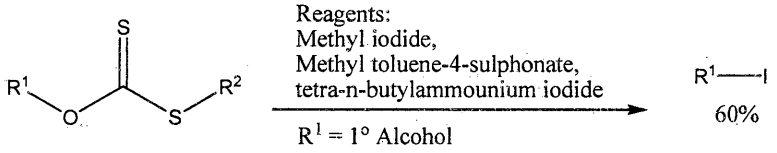
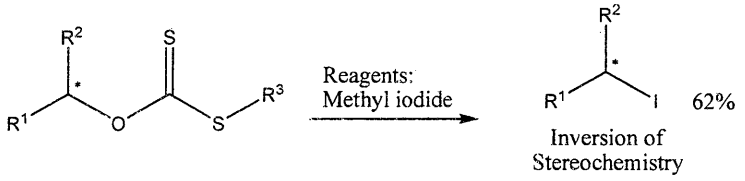
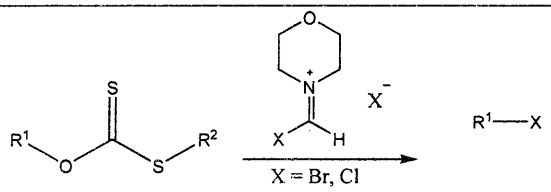
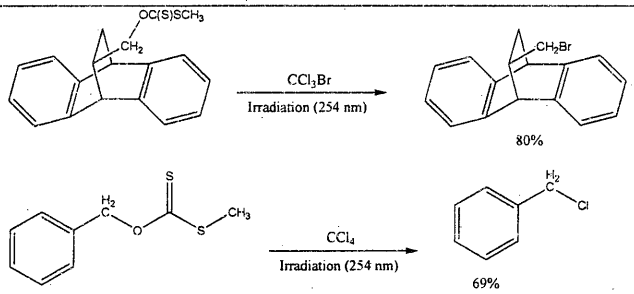
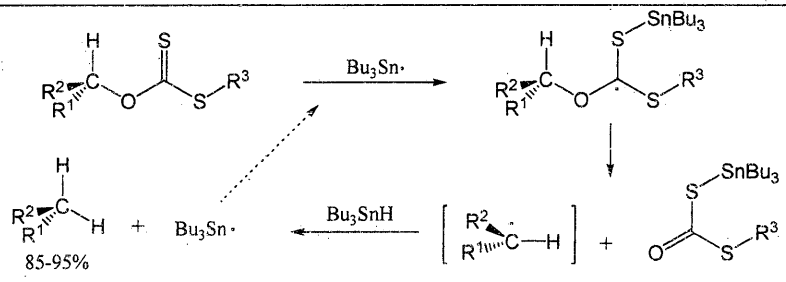


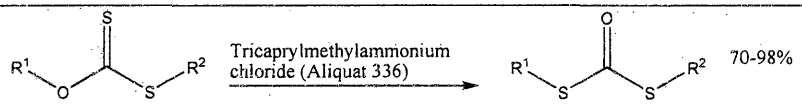
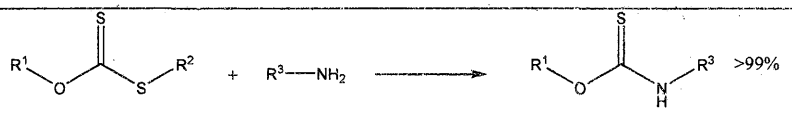
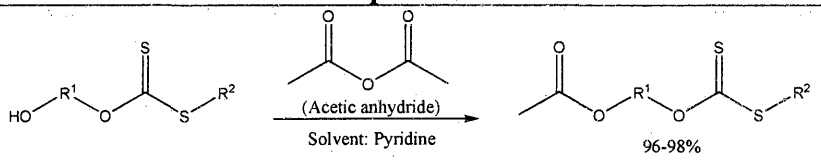
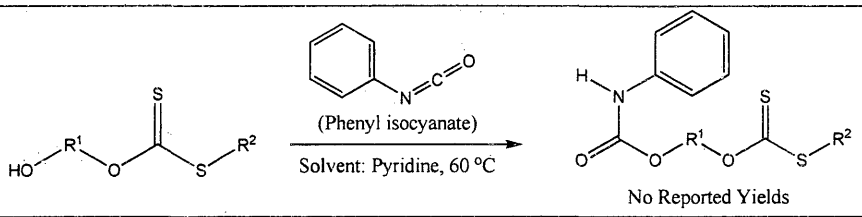
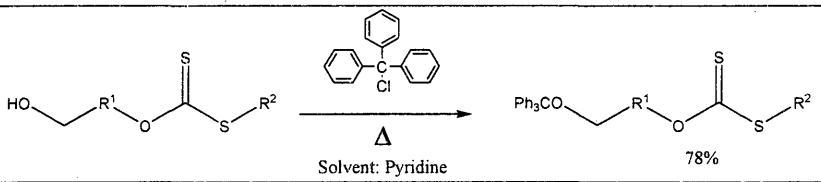
. Provided below in Table 2 is a complete compilation of the deprotective and transformative reactions for Xanthate protected alcohols.

Table 2

Deprotecive Reactions via *O,S*-Dialkylthiocarbonate Intermediate	
Oxidation to Thiocarbonate Ester [15, 16]	 X = H, $OC(O)CH_3$, $OC(O)NHC_6H_5$
Xantahte Oxidation via Benzenetellurinic Anhydride [44]	

Xantahte Oxidation via Benzeneseleninic Anhydride [45]	
Deprotection of Thiocarbonate Ester [15, 16, 18]	
Thiocarbonate Deprotection via $LiAlH_4$ [46]	
Thiocarbonate Deprotection via Silver(I) fluoride [34]	
Transformative Reactions	
Barton Chlorinations of primary xanthate protected alcohols [24]	
Barton Chlorinations of 2° Xanthate protected alcohols with inversion of Stereochemistry [24]	
Chlorination of 2° Xanthate-Protected Alcohols with Retention of Configuration [33]	
PET Reaction [34] (Chlorination)	

Barton Brominations of 1° xanthates [24]	
Barton Brominations of 2° Xanthate protected alcohols with inversion [24]	
Barton Iodination of 1° xanthates [24]	
Barton Iodination of 2° Xanthate protected alcohols with inversion [24]	
Halogenation of Xanthate-Protected Alcohols via Vilsmeier Reagent [28]	
Photolysis of a Xanthate Esters to give Alkyl Halides [27]	
Barton Reduction of Xanthate Protected Alcohols [32]	

Rearrangement of Xanthate Esters to S,S-Dialkyl-dithiocarbonates [37]	
Xanthate Transformation to Thiocarbamates[41]	
Protective Group Additions	
Acetylation [14, 30]	
Carbanilation [16]	
Tritylation [19, 20]	

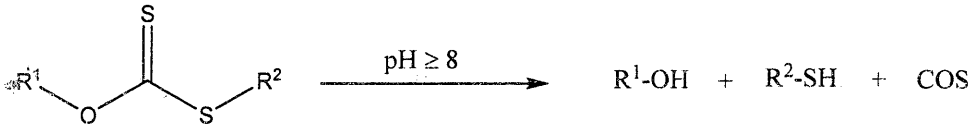
Xanthate Stability in Reaction Conditions

The xanthate moiety, as discussed thus far, is susceptible to a wide array of reactions. Without carefully considering the environmental influences it is probable that the group could react and/or decompose to form an undesirable functionality. However, with accurate planning and foresight conditions can be managed to accommodate for the unique reactivity of the xanthate ester moiety. Four principal factors should be considered when dealing with Xanthates and issues of stability. They are: thermal decomposition, pH stability, oxidative susceptibility, and nucleophilicity.

As discussed in Chapter 1, heating xanthate esters can result in a Chugaev elimination reaction. Although there is considerable substrate-dependant variation in the temperature at which the reaction occurs, a general range for the reaction can be approximated as 100-250 °C.[51] Consequently, to avoid degradation of the protected alcohol the synthetic pathway should not exceed 100 °C.

Despite the fact that most protective procedures are highly basic, hydrolysis can also be a considerable challenge for xanthates. In a relatively recent study, Humeres and co-workers presented work on the hydrolysis of alkyl and cellulose xanthate esters.[52] In their report the group provided a pH profile for the hydrolytic degradation of xanthates that shows a drastic increase in decomposition at a pH ≥ 8. This is extremely useful from a protective viewpoint because the profile is indicative of xanthate stability for aqueous conditions of varying pH.

Figure 24: Hydrolytic Degradation [52]



Consequently, projected reactions for a xanthate protected substrate should maintain a pH range below 8 in order to conserve the xanthate moiety. It should also be noted, however, that the pH profile may vary for xanthate esters with markedly different alkyl substituents.

Oxidation of the xanthate moeity to form the corresponding *O,S*-dialkylthiocarbonate can also be a challenge when dealing with xanthate protected alcohols. The most likely reason, as determined by the work of the Villemin group and confirmed by our studies, is that atmospheric oxidation can occur in significant amounts

given prolonged periods of exposure.[53] This difficulty however can be easily overcome by way of synthesizing, reacting, and storing the xanthate protected alcohols under an inert atmosphere such as nitrogen.

One final important issue to consider when employing xanthates in protective group chemistry is the mild nucleophilic nature of the sulfur in the thiocarbonyl. As reported earlier in work by the Kosma group, methyl triflate reacted more rapidly with the xanthate functionality than the intended free hydroxyl groups.[16] Consequently, considerations must be made whenever a substrate containing a xanthate-protected alcohol is modified with a particularly reactive soft electrophile.

Viability of the Xanthate Ester Protective group

The previously mentioned conditions should not be interpreted as a limitation to the applicability of xanthates as protective groups. It is important to note that there are many compatible reaction conditions that make the group not only viable but quite practical. In future studies, as synthetic chemists continue to develop new drugs and synthetic techniques, there will be an ongoing demand for different protective groups characterized by unique chemical reactivity and stability. The xanthate ester has the potential to play a significant role in the future of protective chemistry.

---

[1] Whitmore, Frank C.; Simpson, C. T. **Some aspects of the Chugaev reaction for dehydrating alcohols.** Journal of the American Chemical Society (1933), 55 3809-12.

[2] Degani, Iacopo; Fochi, Rita. **The phase-transfer synthesis of O,S-dialkyl dithiocarbonates from alkyl halides and alkyl methanesulfonates.** Synthesis (1978), (5), 365-8.

[3] Adams R. et al. **Organic Reactions.** Vol. 12 John Wiley and Sons Inc. 1962. p86-87

[4] Caroll, F. A. **Perspectives on Structure and Mechanisms in Organic Chemistry**. Brooks/Cole Publishing Co., New York. 1998.

[5] Rao, S. R. **Xanthates and Related Compounds**. Marcel Dekker Inc., New York, 1971

[6] Chaturvedi, Devdutt, Ray, Suprabhat. **An Efficient, One-Pot, Triton-B Catalyzed Synthesis of O-Alkyl S-methyl Dithiocarbonates.** Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, India. Monatshefte fuer Chemie (2006), 137(9), 1219-1223.

[7] Paquette, Leo A.; Oplinger, Jeffrey A. **Synthesis of a structurally modified glycal. (-)-(2R,4S)-2-Methyl-2-vinyl-4-(benzyloxy)-3,4-dihydro-2H-pyran.** Journal of Organic Chemistry (1988), 53(13), 2953-9.

[8] Price, Mary E.; Schore, Neil E. **Total synthesis of furanether B.** Journal of Organic Chemistry (1989), 54(24), 5662-7.

[9] Chenevert, Robert; Paquin, Robert; Rodrigue, Andre. **Crown ether catalysis in the synthesis of xanthates.** Synthetic Communications (1981), 11(10), 817-21.

[10] Villemin, Didier; Hachemi, Messaoud. **Potassium fluoride on alumina: a convenient synthesis of O-alkyl methyldithiocarbonates. Pyrolysis of O-benzyl S-methyl dithiocarbonates.** Ecole Nationale Superieure d'Ingenieurs de Caen, I.S.M.R.A., Caen, Fr. Synthetic Communications (1996), 26(13), 2449-2459.

[11] Nagle, Advait S.; Salvatore, Ralph N.; Cross, Richard M.; Kapxhiu, Elona A.; Sahab, Suma; Yoon, Cheol Hwan; Jung, Kyung Woon. **Selective mono protection of diols, diamines, and amino alcohols using cesium bases.** Tetrahedron Letters (2003), 44(30), 5695-5698.

[12] See Chapter 5

[13] Barany, George; Schroll, Alayne L.; Mott, Andrew W.; Halsrud, David A. **A general strategy for elaboration of the dithiocarbonyl functionality , -(C : O) SS -: application to the synthesis of bis (chlorocarbonyl) disulfane and related derivatives of thiocarbonic acids.** Journal of Organic Chemistry (1983), 48(24), 4750-61.

[14] Willard, John J.; Pacsu, Eugene. **Location of xanthate groups in viscose.** Journal of the American Chemical Society (1960), 82 4350-2.

[15] Willard, John J.; Pacsu, Eugene. **New method of removing xanthate groups from carbohydrates. Chemical structure of methyl -D-glucopyranoside monoxanthate.** Journal of the American Chemical Society (1960), 82 4347-50.

[16] Russler, Axel; Lange, Thomas; Potthast, Antje; Rosenau, Thomas; Berger-Nicoletti, Elena; Sixta, Herbert; Kosma, Paul. **A novel method for analysis of xanthate group distribution in viscoses.** Macromolecular Symposia (2005), 223(Cellulose and Cellulose Derivatives), 189-199.

[17] Kihlberg, Jan; Frejd, Torbjoern; Jansson, Karl; Magnusson, Goeran. **Synthetic receptor analogs. Preparation of the 3-O-methyl, 3-C-methyl, and 3-deoxy derivatives of methyl 4-O-.alpha.-D-galactopyranosyl-.beta.-D-galactopyranoside (methyl .beta.-D-galabioside).** . Chem. Cent., Lund Inst. Technol., Lund, Swed. Carbohydrate Research (1986), 152 113-30.

[18] Willard, J. J. **Thiocarbonates as Blocking Groups for the Synthesis of Partial Esters of Carbohydrates**. Canadian Journal of Chemistry (1962), 40 2035-40.

[19] Adamek, E. G.; Purves, C. B. **The location of xanthate groups in partially substituted starch xanthates.** Canadian Journal of Chemistry (1960), 38 2425-32.

[20] Bacque, Eric; El Qacemi, Myriem; Zard, Samir Z. **An Unusual Radical Smiles Rearrangement.** Organic Letters (2005), 7(17), 3817-3820.

[21] Carey, F. and Sundberg, R. **Advanced Organic Chemistry** 4th Ed. Springer, New York, 2000

[22] Moynihan, Meagan F.; Tucker, Joseph F.; Abelt, Christopher J. **Alkyl bromides from dimethylthiocarbonates.** Tetrahedron Letters (Not Published Yet)

[23] (a) 83% Yield: Hegedues, Adrienn; Vigh, Ilona; Hell, Zoltan. **Zeolite-Catalyzed Environmentally Friendly Tetrahydropyranylation of Alcohols and Phenols.** Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, Hung. Synthetic Communications (2004), 34(22), 4145-4152. (b) 92% Yield: Heravi, Majid M.; Behbahani, Farahnaz K.; Oskooie, Hossien A.; Hekmat Shoar, Rahim. **Mild and efficient tetrahydropyranylation of alcohols and dehydropyranylation of THP ethers catalyzed by ferric perchlorate.** Department of Chemistry, School of Sciences, Azzahra University, Tehran, Iran. Tetrahedron Letters (2005), 46(15), 2543-2545. (c) 90% Yield: Mixer, R. Y.; Young, Wm. G. **Allylic rearrangements. XXXV. The reactions of the sodium derivative of allylbenzene in n-pentane with methanol, alkyl and allylic halides.** Univ. of California, Los Angeles, Journal of the American Chemical Society (1956), 78 3379-84.
(d) 96% Yield: Schlama, T.; Gouverneur, V.; Mioskowski, C. **One-step conversion of protected alcohols into alkyl halides using dimethylphosgeniminium salt.** Tetrahedron Letters (1997), 38(20), 3517-3520.

[24] Barton, Derek H. R.; Stick, Robert V.; Subramanian, Raman. **Some reactions of soft electrophiles with esters and other compounds containing the thiocarbonyl group.** Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1976), (19), 2112-16.

[25] Schlama, T.; Gouverneur, V.; Mioskowski, C. **One-step conversion of protected alcohols into alkyl halides using dimethylphosgeniminium salt.** Tetrahedron Letters (1997), 38(20), 3517-3520.

[26] Paquette, Leo A.; Fischer, John W.; Browne, Alan R.; Doecke, Christopher W. **Synthesis of [4] peristylane and functionalized derivatives of this hemispherical ring system.** Journal of the American Chemical Society (1985), 107(3), 686-91.

[27] Cristol, Stanley J.; Seapy, Dave G.. **New procedure for the transformation of alcohols to alkyl halides via xanthate esters and free-radical intermediates.** Journal of Organic Chemistry (1982), 47(1), 132-6. CODEN: JOCEAH ISSN:0022-3263.

[28] See Chapter 4

[29] Cason, James; Correia, John S.. **Investigation of methods for preparing pure secondary alkyl halides.** Journal of Organic Chemistry (1961), 26 3645-9.

[30] Hudson, H. R.. **Factors in the formation of isomerically and optically pure alkyl halides. V. Conditions which determine the formation of 2-halo-2-methyl- and 2-halo-3-methylbutanes in the preparation of 1-halo-2,2-dimethylpropanes from 2,2-dimethylpropan-1-ol.** Journal of the Chemical Society [Section] B: Physical Organic (1968), (6), 664-7.

[31] Jensen, Frederick R.; Moder, Timothy I. **Conversions of alcohols to halides by homolytic reactions.** Journal of the American Chemical Society (1975), 97(8), 2281-3.

[32] Barton, D. H. R.; Motherwell, W. B.. **New and selective reactions and reagents.** Org. Synth.: Today Tomorrow, Proc. IUPAC Symp. Org. Synth., 3rd (1981), Meeting Date 1980, 1-17.

[33] Kozikowski, A. P.; Lee, Jaemoon. **A useful method for converting secondary alcohols to their chlorides with retention of configuration.** Tetrahedron Letters (1988), 29(25), 3053-6. CODEN: TELEAY ISSN:0040-4039. CAN 110:172966 AN 1989:172966 CAPLUS

[34] Barton, Derek H. R.; Dalko, Peter I.; Gero, Stephan D. **Radical cation reactions associated with the thiocarbonyl group.** Tetrahedron Letters (1992), 33(14), 1883-6.

[35] Wuts, P. G. M. and Green, T. W. **Greene's Protective Groups in Organic Chemistry.** 4th Ed. John Wiley and Sons Inc., 2007. p. 297.

[36] Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. **Tris(trimethylsilyl)silane as a radical-based reducing agent in synthesis.** Journal of Organic Chemistry (1991), 56(2), 678-83.

[37] Degani, Iacopo; Fochi, Rita; Regondi, Valeria. **Phase-transfer synthesis of symmetrical S,S-dialkyl dithiocarbonates via O-methyl S-alkyl dithiocarbonates.** Synthesis (1980), (5), 375-8.

[38] Degani, Iacopo; Fochi, Rita; Regondi, Valeria. **Rearrangement of O,S-dialkyl dithiocarbonates to S,S-dialkyl dithiocarbonates catalyzed by tricaprylmethylammonium chloride.** Synthesis (1981), (2), 149-51.

[39] Degani, Iacopo; Fochi, Rita; Regondi, Valeria. **S,S-Dialkyl dithiocarbonates as a convenient source of alkanethiolate anions in phase-transfer-catalysis systems: an improved synthesis of organic sulfides.** Synthesis (1983), (8), 630-2.

[40] Cadamuro, Silvano; Degani, Iacopo; Fochi, Rita; Regondi, Valeria. **S,S-Dialkyl dithiocarbonates as a convenient source of alkanethiols : an improved synthesis of alkylthiocarboxylic acids.** Synthesis (1986), (12), 1070-4.

[41] Khorana, H. G. **Stepwise degradation of peptides.** Cambridge Univ., UK. Chemistry & Industry (London, United Kingdom) 1951, 129.

[42] Barma, D. K.; Bandyopadhyay, A.; Capdevila, Jorge H.; Falck, J. R. **Dimethylthiocarbamate (DMTC): An Alcohol Protecting Group.** Organic Letters (2003), 5(25), 4755-4757.

[43] Barton, Derek H. R.; Finet, Jean Pierre; Thomas, Martial. **Organotellurinic acid anhydrides as selective oxidants in organic synthesis.** Tetrahedron (1986), 42(8), 2319-24.

[44] Cussans, Nigel J.; Ley, Steven V.; Barton, Derek H. R.. **Conversion of thiocarbonyl compounds into their corresponding oxo-derivatives using benzeneseleninic anhydride.** Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1980), (8), 1650-3.

[45] Chochrek, Pawel; Kurek-Tyrlik, Alicja; Michalak, Karol; Wicha, Jerzy. **A new approach to a vitamin D ring C/D building block from the Hajos dione, involving epoxide opening at the more substituted carbon atom.** Tetrahedron Letters (2006), 47(34), 6017-6020.

[46] Roelle, Thomas; Hoffmann, Reinhard W. **Model studies towards the synthesis of the right-hand part of pederin.** Helvetica Chimica Acta (2004), 87(5), 1214-1227.

[47] Tong, Guo-tong; Xie, Jian-wu; Zhou, Xiao-feng. **Study on non-phosgene synthesis of benzyl chloroformate.** Huaxue Shijie (2007), 48(4), 226-227, 231.

[48] West, Christopher W.; Estiarte, M. Angels; Rich, Daniel H. **New Methods for Side-Chain Protection of Cysteine.** Organic Letters (2001), 3(8), 1205-1208.

[49] Mitchell, Helen; Leblanc, Yves. **Amination of Arenes with Electron-Deficient Azodicarboxylates.** Journal of Organic Chemistry (1994), 59(3), 682-7.

[50] Kihlberg, Jan; Frejd, Torbjoern; Jansson, Karl; Magnusson, Goeran. **Synthetic receptor analogs. Preparation of the 3-O-methyl, 3-C-methyl, and 3-deoxy derivatives of methyl 4-O-.alpha.-D-galactopyranosyl-.beta.-D-galactopyranoside (methyl .beta.-D-galabioside).** . Chem. Cent., Lund Inst. Technol., Lund, Swed. Carbohydrate Research (1986), 152 113-30.

[51] March, Jerry. **Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.** 3rd Ed., John Wiley and Sons, New York, 1985, pp 906

[52] Humeres, Eduardo; Soldi, Valdir; Klug, Marilene; Nunes, Mauricea; Oliveira, Celia M. S.; Barrie, Patrick J. **Hydrolysis and aminolysis of alkyl xanthate esters and cellulose analogues.** Canadian Journal of Chemistry (1999), 77(5/6), 1050-1056.

[53] Villemin, Didier; Hachemi, Messaoud. **Potassium fluoride on alumina: a convenient synthesis of O-alkyl methyldithiocarbonates. Pyrolysis of O-benzyl S-methyl dithiocarbonates.** Ecole Nationale Superieure d'Ingenieurs de Caen, I.S.M.R.A., Caen, Fr. Synthetic Communications (1996), 26(13), 2449-2459.

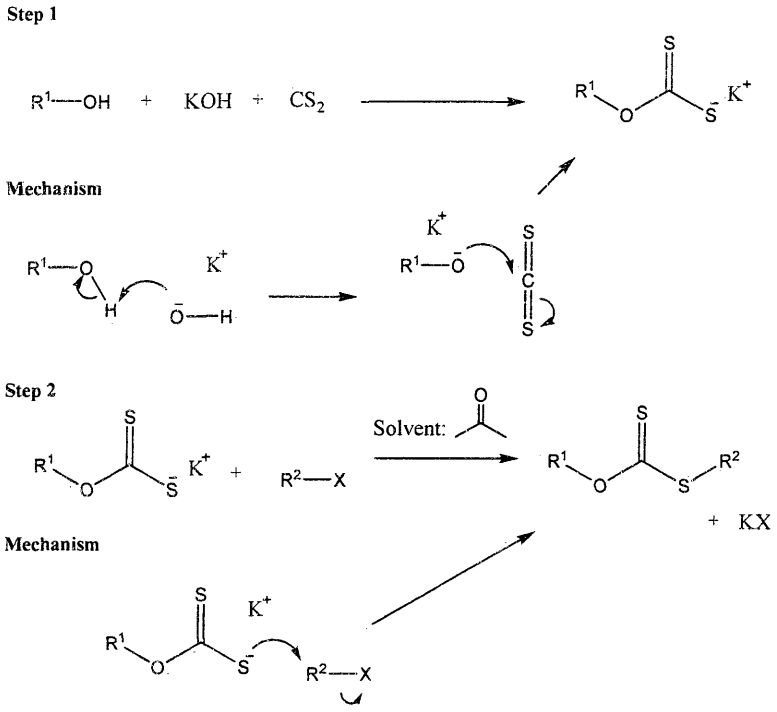
Chapter 3

An Experimental Study of Xanthate Synthesis

Introduction and Theory

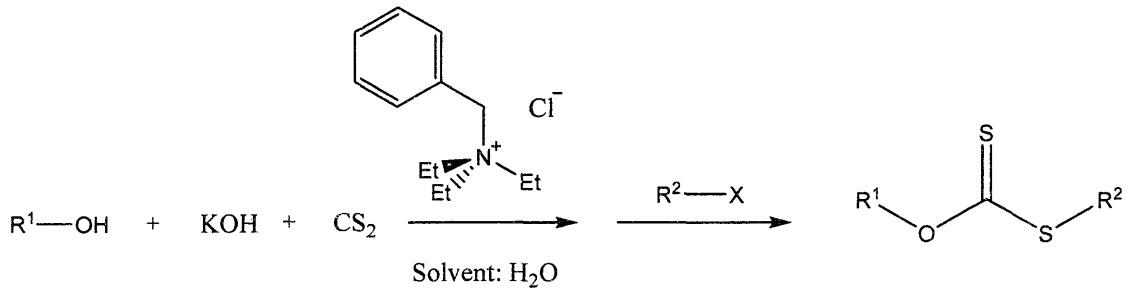
As discussed in Chapter 2, there are a variety of different methods available for the xanthate protection of alcohols. Since our primary research focus was on the transformative reactions of xanthate esters with the Vilsmeier reagent we choose to employ two simple and efficient methods in order to synthesize 12 different xanthate esters. Method 1, shown below in Figure 1, is a conventional two step method of xanthate synthesis. The first step involves the deprotonation of an alcohol to give a nucleophilic alkoxide, which then reacts with carbon disulfide (electrophile) to produce a yellow Xanthate salt. The second step involves a simple S_N2 displacement reaction in which the xanthate salt acts as a nucleophile to displace a halide anion from a haloalkane to produce the desired xanthate.

Figure 1: Synthetic Method 1 (Conventional Xanthate Synthesis)



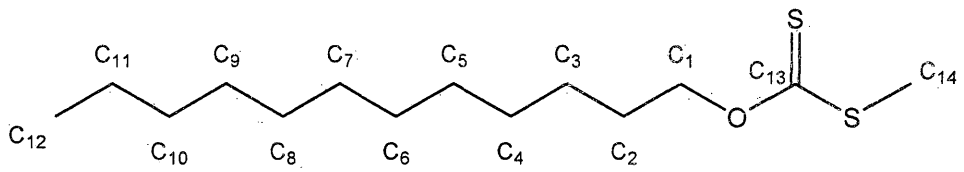
The second technique used for synthesizing xanthates, Method 2 (Figure 2), is an adaptation of a phase transfer synthesis reported by Degani and co-workers.[1] In this procedure the reaction is carried out in a single reaction pot under phase transfer conditions and catalyzed by a phase exchange salt. This simplification allows for a more efficient and economical reaction in which only one workup is required. The phase exchange catalyst, a quaternary ammonium salt, is added in order to promote the phase transition that occurs as the substrate changes from an aqueous ionic reactant to a non-polar organic product. Mechanistically, Method 2 is identical to that of Method 1.

Figure 2: Synthetic Method 2 (Condensed Xanthate Synthesis)



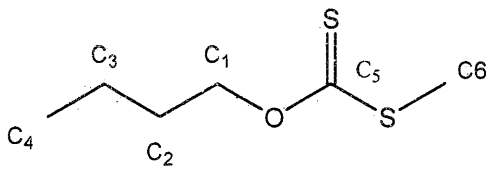
Experimental

All procedures below are for a 10 mmol scale. GC-MS characterizations were completed using an *Agilent Technologies Model 5973 Network Mass Selective Detector* (GC-MS system) coupled with *Hewlett-Packard* processing capabilities. ^{1}H-NMR and ^{13}C-NMR spectra were standardized to tetramethylsilane and chemical shifts were recorded in ppm and Hz. The data was obtained using a *Varian Mercury 400VX Model* (400 MHz) Cryogenic NMR with *Varian VNMR 6.1B* programming and *NUTS 1D* NMR data processing.



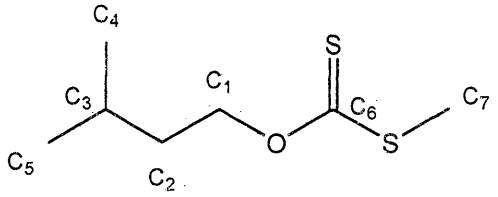
Xanthate I: *O*-dodecyl-*S*-methylxanthate

Experimental Procedure: Potassium hydroxide pellets (0.62 g) were ground into a fine powder and transferred into a round bottom flask with a magnetic stir bar. Dodecan-1-ol (1.86 g) was then added followed by stirring and slight heat (< 60 °C). After the potassium hydroxide dissolved completely the solution was cooled to 0 °C and carbon disulfide (0.60 mL) was added drop-wise. After 2 hours the solution was diluted with ethyl ether and crystals were isolated via vacuum filtration. The crystals, a potassium xanthate salt, were then dissolved in warm acetone (50 mL) and decanted leaving a dense red oil impurity. The solution was then condensed to 25 mL, transferred to a round bottom flask and cooled to 0 °C in an ice bath. A separate solution of acetone (10 mL) and iodomethane (0.62 mL) was prepared and added dropwise to the reaction flask with stirring. The reaction stirred for 2 hours after which a white precipitate (potassium iodide) was removed by gravity filtration. The acetone solvent was then evaporated under aspirator vacuum and the remaining oil was dissolved into petroleum ether (50 mL). This solution was washed once with ice water, once with ice cold 10% sulfuric acid solution, and once again with ice water (75 mL each). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. **I** was isolated in 61% yield via fractional distillation under 0.3 torr with a boiling point of 135 °C. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 1-3).



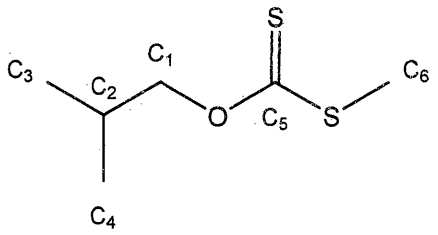
Xanthate II: *O*-butyl-*S*-methylxanthate

Experimental Procedure: Potassium *O*-butylxanthate (1.88 g) was transferred into a round bottom flask with a magnetic stir bar. Acetone (50 mL) was then added and stirred to dissolve the salt. After the salt is dissolved the reaction mixture was cooled to 0 °C. Separately a solution of acetone (10 mL) and iodomethane (0.62 mL) was prepared and added slowing by way of addition funnel to the reaction flask. The reaction stirred for 2 hours after which a white precipitate (potassium iodide) was removed by gravity-filtration. The solvent, acetone, was then evaporated under aspirator vacuum and the reaming oil was dissolved into petroleum ether (50 mL). This solution was washed once with ice water, once with ice cold 10% sulfuric acid solution, and once again with ice water (75 mL each). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. **II** was isolated in 81% yield via fractional distillation under 0.3 torr with a boiling point of 60 °C. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 4-6).



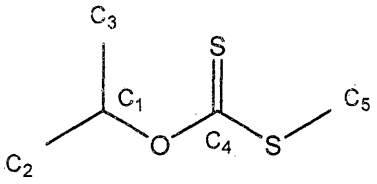
Xanthate III: *O*-(3-methylbutyl)-*S*-methylxanthate

Experimental Procedure: Potassium *O*-(3-methylbutyl)-xanthate (2.00 g) was transferred into a round bottom flask with a magnetic stir bar. Acetone (50 mL) was then added and stirred to dissolve the salt. After the salt is dissolved the reaction mixture was cooled to 0 °C. Separately a solution of acetone (10 mL) and iodomethane (0.62 mL) was prepared and added slowing by way of addition funnel to the reaction flask. The reaction stirred for 2 hours after which a white precipitate (potassium iodide) was removed by gravity filtration. The solvent, acetone, was then evaporated under aspirator vacuum and the reaming oil was dissolved into petroleum ether (50 mL). This solution was washed once with ice water, once with ice cold 10% sulfuric acid solution, and once again with ice water (75 mL each). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. **III** was isolated in 83% yield via fractional distillation under 0.3 torr with a boiling point of 43 °C. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 7-9).



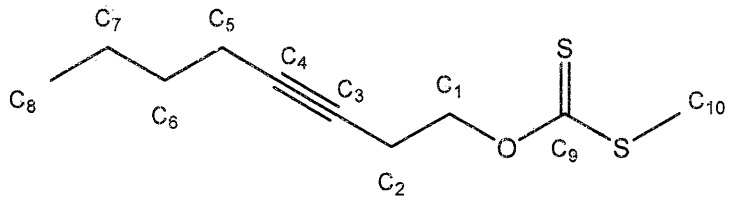
Xanthate IV: *O*-(2-methylpropyl)-*S*-methylxanthate

Experimental Procedure: Potassium *O*-(2-methylpropyl)-xanthate (1.88 g) was transferred into a round bottom flask with a magnetic stir bar. Acetone (50 mL) was then added and stirred to dissolve the salt. After the salt is dissolved the reaction mixture was cooled to 0 °C. Separately a solution of acetone (10 mL) and iodomethane (0.62 mL) was prepared and added slowing by way of addition funnel to the reaction flask. The reaction stirred for 2 hours after which a white precipitate (potassium iodide) was removed by gravity filtration. The solvent, acetone, was then evaporated under aspirator vacuum and the reaming oil was dissolved into petroleum ether (50 ml). This solution was washed once with ice water, once with ice cold 10% sulfuric acid solution, and once again with ice water (75 ml each). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. **IV** was isolated in 65% yield via fractional distillation under 0.3 torr with a boiling point of 33 °C. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 10-12).



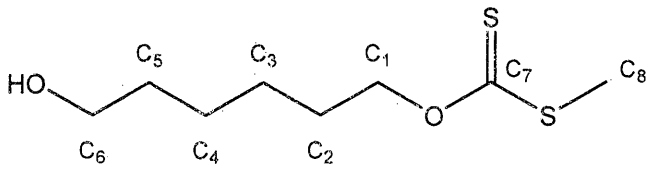
Xanthate V: *O*-(1-methylethyl)-*S*-methylxanthate

Experimental Procedure: Potassium *O*-(1-methylethyl)-xanthate (1.74 g) was transferred into a round bottom flask with a magnetic stir bar. Acetone (50 mL) was then added and stirred to dissolve the salt. After the salt is dissolved the reaction mixture was cooled to 0 °C. Separately a solution of acetone (10 mL) and iodomethane (0.62 mL) was prepared and added slowing by way of addition funnel to the reaction flask. The reaction stirred for 2 hours after which a white precipitate (potassium iodide) was removed by gravity-filtration. The solvent, acetone, was then evaporated under aspirator vacuum and the reaming oil was dissolved into pet ethe r (50 mL). This solution was washed once with ice water, once with ice cold 10% sulfuric acid solution, and once again with ice water (75 mL each). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. **V** was isolated in 61% yield via fractional distillation under 0.3 torr with a boiling Point of 26 °C. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 14-16)



Xanthate VI: *O*-(oct-3-ynyl)-*S*-methylxanthate

Experimental Procedure: To a round bottom flask oct-3-yn-1-ol (1.26 g) and H_2O (15 mL) were added with stirring. Potassium hydroxide pellets (0.62 g) were ground into a fine powder and transferred into the reaction flask. Benzyltriethylammonium chloride (0.5 g) was then added and the solution was heated (< 60 °C) to ensure that all solids had dissolved. The flask was then cooled to 0 °C and carbon disulfide (0.60 mL) was added using a syringe. The mixture returned to room temperature while stirring for two hours at which time the solution was an orange/yellow liquid. The reaction flask was then re-cooled to 0 °C and iodomethane (0.62 mL) was added dropwise via addition funnel. The step is exothermic and should be carried out with care. The reaction then stirred for 2 hours, leaving a yellow solution composed of an upper aqueous layer and a dense organic oil layer on the bottom. The contents of the flask were transferred into a separatory funnel and acidified with 10 % sulfuric acid (50 mL). The aqueous layer became colorless and the yellow organic layer was extracted out into diethyl ether (50 mL). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. **VI** was isolated in 44% yield via fractional distillation under 0.3 Torr with a boiling point of 99-101 °C. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 18-20).

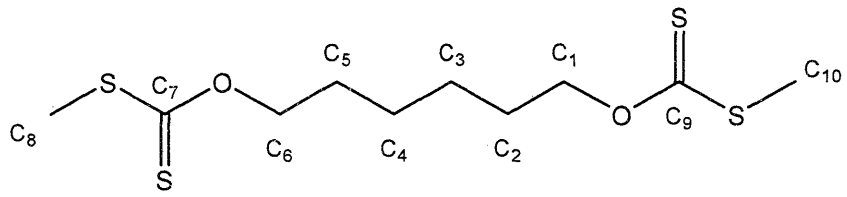


Xanthate VII: *O*-(6-hydroxyhexyl)-*S*-methylxanthate

Experimental Procedure: To a round bottom flask 1,6-hexanediol (1.18 g) and H_2O (10 mL) were added with stirring. Potassium hydroxide (0.67 g) and benzyltriethylammonium chloride (0.50 g) were then added and the solution was heated to dissolve all solids. The reaction flask was cooled to 0 °C and carbon disulfide (0.60 mL) was added dropwise via syringe. The mixture was allowed to return to room temperature while stirring for 2 hours, at which time the solution was an orange/yellow liquid. The reaction flask was then re-cooled to 0 °C and Iodomethane (0.62 mL) was added dropwise via addition funnel. The reaction stirred for 2 hours, leaving a yellow solution composed of an upper aqueous layer and a dense organic layer on the bottom. The contents of the flask were then transferred into a separatory funnel and acidified with 10 % sulfuric acid (50 mL). The aqueous layer became colorless and the yellow organic layer was extracted out into diethyl ether (50 mL). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. GC-MS anaylsis of this oil showed the product **VII** as well as the *bis* xanthate (**VIII**) and dimethyl trithiocarbonate. Separation was accomplished via silica gel column chromatography. Hexanes were used to wash out **VIII** and dimethyl trithiocarbonate. Dichloromethane washed out **VII**. A gradient was unnecessary in the solvent transition. Concentration of the solvent gave **VII** in 34% yield. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-

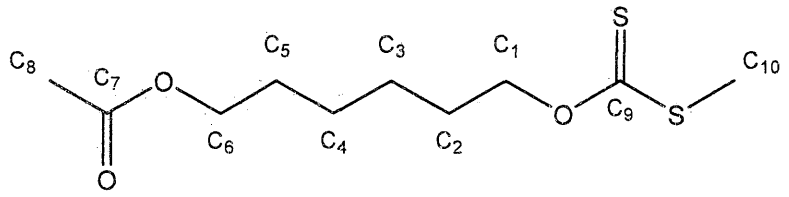
NMR, and GC-MS (Figures A 21-24). It should also be noted that in other synthetic reactions of **VII** vacuum distillation at 0.3 Torr was used for isolation, however the high boiling points of the xanthate products made distillation difficult because of product degradation. When this method was successful, the boiling points were found to be 115 °C for **VII** and 200-210 °C for **VIII**. (Figures A 21-24)

Failed Procedure: The procedure was identical to the experimental procedure directly above with the exception that the reaction mixture was stirred for 8 hours prior to addition of iodomethane. The reaction solution after 8 hours of stirring was not the characteristic orange/yellow color, rather a dark red color. GC-MS analysis of reaction pot after addition of iodomethane showed 91% dimethyl trithiocarbonate with **VII** present at 9%. The gas chromatograph is given in Figure A 25.



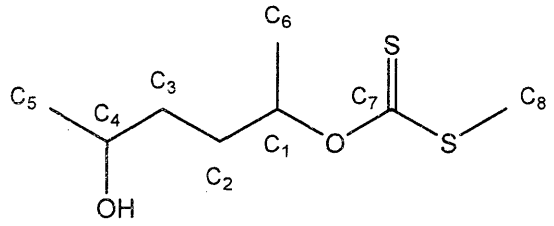
Xanthate VIII: *S,S'*-dimethyl *O,O'*-hexane-1,6-diyl dicarbondithioate

Isolation Procedure: VIII was recovered as a side product in the synthesis of **VII**. The hexane washes from the silica gel column were concentrated on a Rotovap to give a viscous yellow oil composed of both **VIII** and the impurity dimethyl trithiocarbonate. Removal of Dimethyl trithiocarbonate was accomplished via fractional distillation under 0.3 Torr in which all the distillation pot was heated at 34-50 °C. Pure **VIII** remained in the pot as a yellow solid, giving a yield of 14%. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figure A 26-29).



Xanthate IX: *O*-(6-acetoxyhexyl)-*S*-methylxanthate

Isolation Procedure: IX was recovered as a side product during the synthesis of **VII**. Initial attempts to isolate **VII** involved the use of ethyl acetate as a solvent in the silica gel column. In these conditions a transesterification reaction occurred producing a mixture of **IX**, **VII**, and ethanol. Separation of **IX** and **VII** was accomplished by way of column chromatography with a silica gel stationary phase. Pure Hexanes washed **IX** from the column and Dichloromethane eluted out **VII**. A gradient was unnecessary in the solvent transition. A crude calculation of yield based on recovered **VII** and **IX** gave a 19% yield.

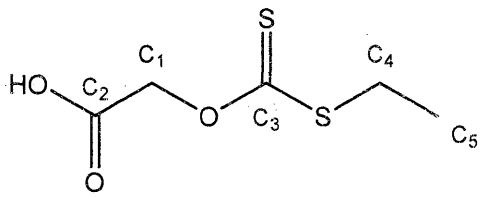


Xanthate X: *O*-(4-hydroxy-1-methylpentyl)-*S*-methylxanthate

Experimental Procedure: To a round bottom flask 2,5-hexanediol (1.18 g) and H_2O (10 mL) were added with stirring. Potassium hydroxide (0.67 g) and benzyltriethylammonium chloride (0.50 g) were then added and the solution was heated to dissolve all solids. The reaction flask was cooled to 0 °C and carbon disulfide (0.60 mL) was added dropwise via syringe. The mixture was allowed to return to room temperature

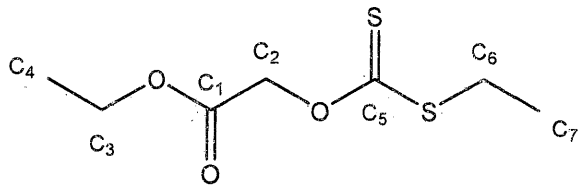
while stirring for 2 hours, at which time the solution was an orange/yellow liquid. The reaction flask was then re-cooled to 0 °C and iodomethane (0.62 mL) were added dropwise via addition funnel. The reaction stirred for 2 hours, leaving a yellow solution composed of an upper aqueous layer and a dense organic layer on the bottom. The contents of the flask were then transferred into a separatory funnel and acidified with of 10 % sulfuric acid (50 mL). The aqueous layer became colorless and the yellow organic layer was extracted out into diethyl ether (50 mL). The ether layer was then dried with sodium sulfate and concentrated on a Rotovap to give a yellow oil. GC-MS anaylsis of this oil showed the product, **X** as well as the impurity dimethyl trithiocarbonate. Separation was accomplished via silica gel column chromatography. Hexanes were used to elute dimethyl trithiocarbonate. Dichloromethane washed out **X**. A gradient was unnecessary in the solvent transition. Concentrating the solvent via Rotovap gave **X** in 34% yield. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 36-38).

Failed Procedure: The procedure was identical to the experimental procedure directly above with the exception that the reaction mixture was stirred for 8 hours prior to addition of iodomethane. The reaction solution after 8 hours of stirring was not the characteristic orange/yellow color, rather a dark red color. GC-MS analysis of reaction pot after addition of iodomethane showed only dimethyl trithiocarbonate. **X** was not present in any detectable amount. The gas chromatograph is given in Figure A 39.



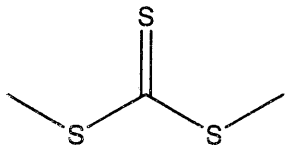
Xanthate XI: *O*-(2-carboxyethyl)-*S*-ethylxanthate

Experimental Procedure: To a round bottom flask 2,5-hexanediol (0.76 g) and H_2O (10 mL) were added with stirring. Potassium hydroxide (1.2 g) and benzyltriethylammonium chloride (0.50 g) were then added and the solution was heated to dissolve all solids. The reaction flask was cooled to 0 °C and carbon disulfide (0.60 mL) was added dropwise via syringe. The mixture was allowed to return to room temperature while stirring for 2 hours, at which time the solution was an orange/yellow liquid. The reaction flask was then re-cooled to 0 °C and iodomethane (0.62 mL) was added dropwise via addition funnel. The reaction stirred for 2 hours, leaving a yellow solution. The contents of the flask were then transferred into a separatory funnel and washed twice with ethyl ether (50 mL) to remove diethyl trithiocarbonate. The aqueous layer was then acidified with of 10 % sulfuric acid (50 mL), and **XI** was extracted with petroleum ether (2 x 50 mL). The petroleum ether solution was then dried with sodium sulfate and concentrated on a rotovap to give a yellow oil. GC-MS analysis of this oil showed the pure **XI** and a small amount of diethyl trithiocarbonate. Separation was accomplished via fractional distillation under 0.3 Torr with diethyl trithiocarbonate boiling over at 80-82 °C and **XI** boiling over at 123-126 °C. **XI** is a pale yellow solid and the yield was determined to be 53%. Compound identities were confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 40-45).



Xanthate XII: *O*-(acetic acid ethylester)-*S*-ethylxanthate

Experimental Procedure: The esterification **XI** of was carried out using a procedure taken from Oniscu and co-workers.[2] **XI** (1.80 g) and Dowex HCRW-2 H+ cation exchange resin (0.919 g) were added to a 100 mL round bottom flask followed by the addition of absolute (200 proof) ethanol (15 mL). The mixture was refluxed for 10 hrs at 90-95 °C. The subsequent reaction mixture was then dried with sodium sulfate and filtered by gravity. Excess ethanol was removed via Rotovap and the remaining mixture was distilled under vacuum at 0.3 Torr. Diethyl trithiocarbonate distilled over at 80-82 °C and **XII** co-distilled 83-110 °C. The remaining yellow liquid in the pot was collected and determined to be pure **XII**. Product yield was 10% and identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 46-48).



Dimethyl trithiocarbonate

Synthetic Study: A test reaction was run to determine if dimethyl trithiocarbonate was made in competition with xanthates during the Method 2 procedure. All reagents where measured to 10 mmol. Potassium hydroxide (0.56 g) was added to a 50 mL round bottom flask containing de-ionized water (10 mL) and the contents were mixed with a magnetic

stir bar. Carbon disulfide (0.60 mL) and iodomethane (0.62 mL) were then added and the reaction pot was left stirring for 12 hours. At that point of workup the reaction flask contained three layers, a yellow organic bottom layer, a colorless aqueous layer in the middle, and a small layer of unreacted carbon disulfide on top. The contents were transferred to a separatory funnel and acidified with of 10% sulfuric acid (50 mL). Two extractions with diethyl ether (50 mL each) removed the yellow organic layer. The diethyl ether was then concentrated on a Rotovap, leaving a pure sample of dimethyl trithiocarbonate. Product yield was 32% and identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 49-52).

Xanthate Synthesis: Results and Discussion

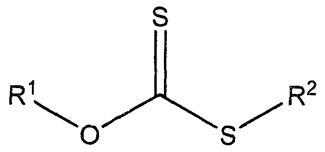


Table 1: Synthesis Results

Xanthate	R_1	R_2	Method	% Yield (7)	BP (°C at 0.3 torr)
I	$-(CH_2)_{11}CH_3$	$-CH_3$	1	61	135
II	$-(CH_2)_3CH_3$	$-CH_3$	1	81[a]	60
III	$-CH_2CH_2CH(CH_3)_2$	$-CH_3$	1	83[a]	43
IV	$-CH_2CH(CH_3)_2$	$-CH_3$	1	65[a]	33
V	$-CH(CH_3)_2$	$-CH_3$	1	61[a]	26
VI	$-CH_2CH_2C{\equiv}CCH_2CH_2CH_2CH_3$	$-CH_3$	2	44	99-101
VII	$-(CH_2)_6OH$	$-CH_3$	2	34	115[b]
VIII	$-(CH_2)_6OC(S)SCH_3$	$-CH_3$	2	14[c]	200-210[b]
IX	$-(CH_2)_6OC(O)CH_3$	$-CH_3$	2	19[c]	-
X	$-CH(CH_3)CH_2CH_2CH(OH)CH_3$	$-CH_3$	2	34	>100[b]
XI	$-CH_2C(O)OH$	$-CH_2CH_3$	2	53	123-126
XII	$-CH_2C(O)OCH_2CH_3$	$-CH_2CH_3$	-	10	-

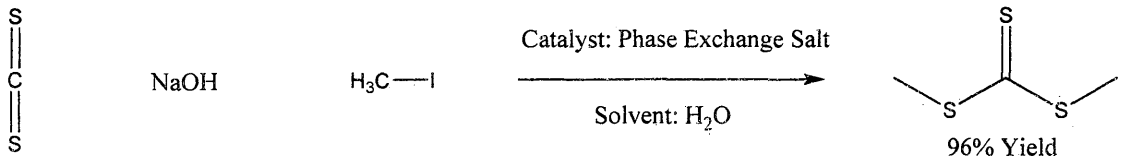
[a] Yields for Xanthates II – V only account for Step 2 of the Conventional Synthesis (Method 1), [b] Significant amount of compound degrades a this temperature, [c] Additional studies are necessary to obtain correct yield

No comparative study was done on any one xanthate to determine which procedural method was more effective. However, the general trend, as shown in Table 1, indicates that Method 1 may give higher yields. Further investigation is necessary for confirmation.

The synthetic reactions for I-V were carried out using Method 1, which produced pure products with relatively high yields. The procedure however was cumbersome and significantly more time consuming than Method 2 which was adopted for VI-XI. A significant challenge with Method 2, however, was the byproduct dimethyl trithiocarbanate, a viscous yellow liquid that co-distills with smaller xanthates. Consequently, Method 1 proved to be the most effective way to obtain pure samples of II, III, IV, and V.

In an effort to determine the cause for the byproduct, test studies where run. It was determined that aqueous sodium hydroxide in the presence of carbon disulfide and iodomethane reacted to give dimethyl trithiocarbonate. Given this finding and the relatively poor yields reported for Method 2, it is evident that a competition reaction was occurring. A literature search in synthetic methods confirmed these findings. Figure 3 is a procedure reported by Lee and co-workers for the synthesis of dimethyl trithiocarbonate.[3]

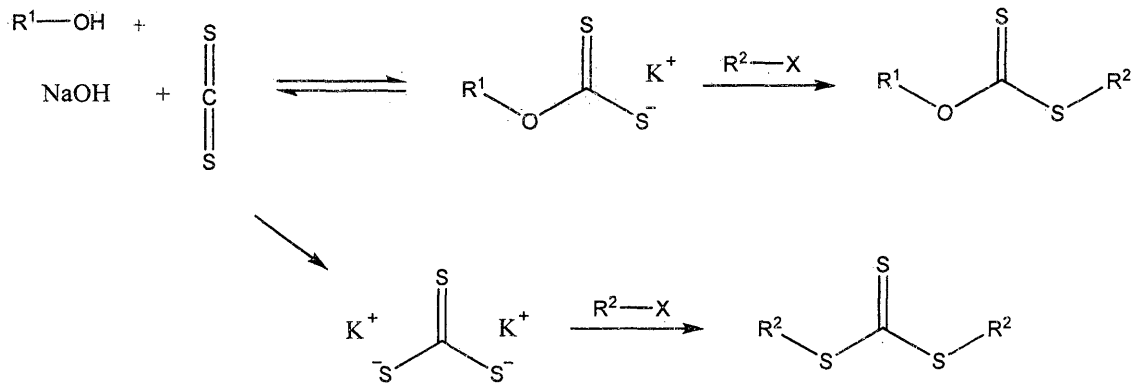
Figure 3: Synthesis of Dimethyl Trithiocarbonate[3]



The reaction conditions given above in Figure 3 are almost identical to the reaction conditions for Method 2 (Figure 2). The only exception is that the xanthate synthesis has the substrate alcohol present as well. Additional evidence to support this can be sited to the orange color of the reaction mixture just prior to the addition of the alkyl halide (**VI-XI**). In their study, Lee and co-works reported that hydroxide reacts with carbon disulfide to form trithiocarbonate anion, a blood-red oil, which then reacts with 2 equivalents of akyl halide.[3] The orange color is likely a mixture of trithiocarbonate anion (blood-red) and the yellow xanthate salt. It should also be noted that the dense red oil impurity left behind in the synthesis of I is also the trithiocarbonate anion. This separation step (see synthesis of **I**) is the likely cause for the absence of the dimethyl trithiocarbonate byproduct in Method 1.

One final observation in regards to the dimethyl trithiocarbonate byproduct is that there is evidence suggesting that Method 2 involves an equilibrium that favors the formation of the trithiocarbonate anion over the xanthate salt anion. This fact became evident over the course of many reactions where variations in time prior to the addition of the alkyl halide corresponded to variations in the color of the reaction mixture. The initial observed color after addition of carbon disulfide is yellow and as time progresses it becomes more orange until approximately 4 hours when the color is red. The failed synthetic reaction of **X** was allowed to stir for 8 hours before the addition. The reaction gave only dimethyl trithiocarbonate with no detectable xanthate. The failed synthetic reaction of **VII** also gave almost identical results. Though more work is necessary to confirm our predictions, the Figure 4 depicts a likely reaction pathway.

Figure 4: Pathway for Synthesis of Dimethyl trithiocarbonate



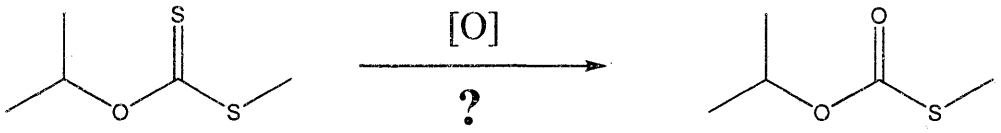
With this pathway the xathate salt forms initially, but, given enough time, the trithiocarbonate salt forms as well. Moreover, the xanthate salt is in equilibrium with and, if not consumed, may decompose back to form the initial reactants, resulting in more trithiocarbonate salt. A simple adjustment would be to add the alkyl halide in the initial step which should eliminate the equilibrium due to immediate consumption of the xanthate salt in the S_N2 displacement.

Three of the synthesized xanthates (**VII**, **VIII**, and **IX**) have not been reported in literature. Samples of these compounds were sent to Old Dominion University for additional confirmation by way of High Resolution Mass Spectral Analysis. The samples where dissolved in 1:1 THF:MeOH with NaCl and analyzed by positive ion electrospray on a Bruker 12 Tesla APEX -Qe FTICR-MS with an Apollo II ion source. The spectra are presented in Figures A 24, 29, and 33.

An interesting discovery was made when ^{13}C-NMR analysis of **X** revealed that the product is actually a diastereomeric mixture. This fact is evident in that there are two distinguishable peaks for all the component carbon atoms involved in the stereocenter. The only exception is the peak for C_6 which integrates for twice the value of the other carbons. Though peak intensities in ^{13}C-NMR are generally highly variable, it seems likely that this peak is simply an overlap of the two diastereometric carbons at the sixth position. Additional analysis of the orginal alcohol substrate revealed the reactant to be a mixture of the *meso*-diastereomer, (S,R)-2,5-hexanediol, and the enantiomers, (R,R)- 2,5-hexanediol and (S,S)- 2,5-hexanediol (Figures A 34-35). The ratio of diastereomeric peak intensities was approximately identical for both the alcohol substrate and the xanthate product which is an indication that there is no diastereomeric preference involved in the reaction.

One final concern, which became apparent after numerous synthetic reactions was the issue of xanthate ester oxidation. On numerous occasions, our group observed that slight variations in workup procedures as well as prolonged storage resulted in the conversion of the xanthate ester to its *O,S*-dialkyl thiocarbonate derivative. Shown in Figure 5 below is a representation of the oxidative conversion of **V**. A stored sample demonstrating oxidation was also analyzed and the gas chromatograph and mass spectra are given in Figure A 13 and Figures A 16-17 respectively.

Figure 5: Oxidation of V to *O*-(1-methylethyl)-*S*-methylthiocarbonate



V *O*-(1-methylethyl)-*S*-methylthiocarbonate

Oxidative conversion becomes most obvious when the samples are characterized via GC-MS. The gas chromatograph for **V** shows the thiocarbonate derivative eluting off the column approximately 1.5 minutes prior to the xanthate. There are also two distinct differences in the respective mass spectra. The molecular ion for the thiocarbonate is 16 amu less than that of the xanthate, and the fragmentation pattern for the methy thiocarbonate functionality gives a cation fragment of 75 amu, which is also 16 amu less than the 91 amu xanthate cation fragment. The rest of the fragments in the mass spectrum are essentially identical due to the fact that alkyl substituents are conserved during oxidation.

Previous works in the literature have shown that xanthates can be oxidized to give thiocarbonates in high yields through both anionic oxidation or via an oxidizing reagent such as hydrogen peroxide.[4, 5] The exact source of oxidation in this study is unknown. However, I believe that it is likely a result of exposure to oxygen in the atmosphere. Results similar to our study have been reported by Villemin and co-workers, in which oxidative side-reactions in their xanthate synthetic studies gave thiocarbonates with yields as high as 15%.[6] The Villemin group also reported that oxidation during the synthesis of xanthates was avoided when preformed in an inert nitrogen atmosphere.[6] This report confirms our hypothesis, but because the Villemin group used a different

synthetic method it is necessary that a separate study be done to state conclusively that this is the source of contamination.

Conclusion

As a synthetically useful protective procedure, Methods 1 and 2 are largely ineffective. In fact, there are many other procedures (discussed in chapter 2) which provide much more acceptable yields and are still similar in general methodology. This study does, however, provide an interesting insight into the potential complications faced when working with protective procedures that utilize a hydroxide base to form the initial alkoxide. Furthermore, for procedures in which a loss of the initial alcohol substrate is not a significant obstacle, these simple methods are quite effective. Other methods for generating the alkoxide intermediate, for instance sodium hydride, may be used for more complex and expensive alcohol substrates.

[1] Degani, Iacopo; Fochi, Rita. **The phase-transfer synthesis of O,S-dialkyl dithiocarbonates from alkyl halides and alkyl methanesulfonates.** Synthesis (1978), (5), 365-8.

[2]Oniscu, Corneliu; Bancila, Virgiliu; Ionescu, Jan Corneliu; Botezatu, Viorica; Cascaval, Dan. **Esterification process for the preparation of alkyl 2,4-dichlorophenoxyacetates.** Rom. (1997), 3 pp.

[3]Lee, Albert W. M.; Chan, W. H.; Wong, H. C. **One pot phase transfer synthesis of trithiocarbonates from carbon disulfide and alkyl halides.** Dep. Chem., Hong Kong Baptist Coll., Kowloon, Hong Kong. Synthetic Communications (1988), 18(13), 1531-6.

[4] Batanero, Belen; Picazo, Oscar; Barba, Fructuoso. **Facile and Efficient Transformation of Xanthates into Thiocarbonates by Anodic Oxidation.** Journal of Organic Chemistry (2001), 66(1), 320-322.

[5] Silvester, Ewen; Truccolo, David; Hao, Fu Ping. **Kinetics and mechanism of the oxidation of ethyl xanthate and ethyl thiocarbonate by hydrogen peroxide.** Journal of the Chemical Society, Perkin Transactions 2 (2002), (9), 1562-1571.

[6] Villemin, Didier; Hachemi, Messaoud. **Potassium fluoride on alumina: a convenient synthesis of O-alkyl methyldithiocarbonates. Pyrolysis of O-benzyl S-methyl dithiocarbonates.** Ecole Nationale Superieure d'Ingenieurs de Caen, I.S.M.R.A., Caen, Fr. Synthetic Communications (1996), 26(13), 2449-2459.

Chapter 4

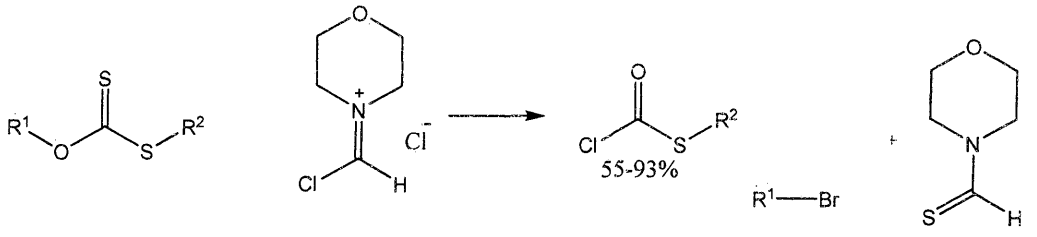
The Transformation of Xanthate Protected Alcohols via the Vilsmeier Reagent

Vilsmeier Reagent

The method of direct conversion of a protected alcohol to the corresponding alkyl halide has been shown to be an important and useful step in synthetic organic chemistry.[1,2,3] Previous work by Barton and co-workers has also shown that xanthate esters can react with a variety of mild electrophilic reagents to give alkyl halides.[4] However, their work as well as many of the current procedures for the transformation of xanthate esters (see chapter 2) fail to maintain the level of wide-ranging utility necessary to be viable as a general synthetic technique. Other chemists have attempted to use radical reactions to obtain better results but again these methods are not broadly applicable and they often involve radical intermediates that result in racemization of stereocenters.

In recent studies, Abelt and co-workers have demonstrated that xanthates react well with Vilsmeier reagent to produce *S*-alkyl chlorothioformates in good yields.[5]

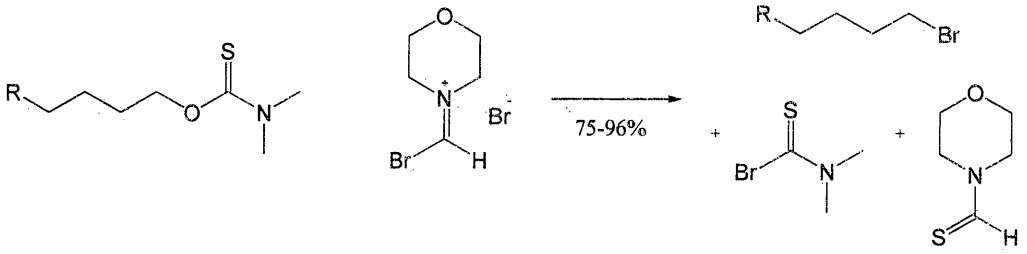
Figure 1: Synthesis of *S*-alkyl chlorothioformates[5]



An interesting byproduct of this reaction was also determined to be the alkyl halide derivative of the original alcohol substrate. This discovery indicated that the Vilsmeier reagent may prove to be a potentially useful transformative reagent for xanthate protected alcohols. Our group then focused on to this subject

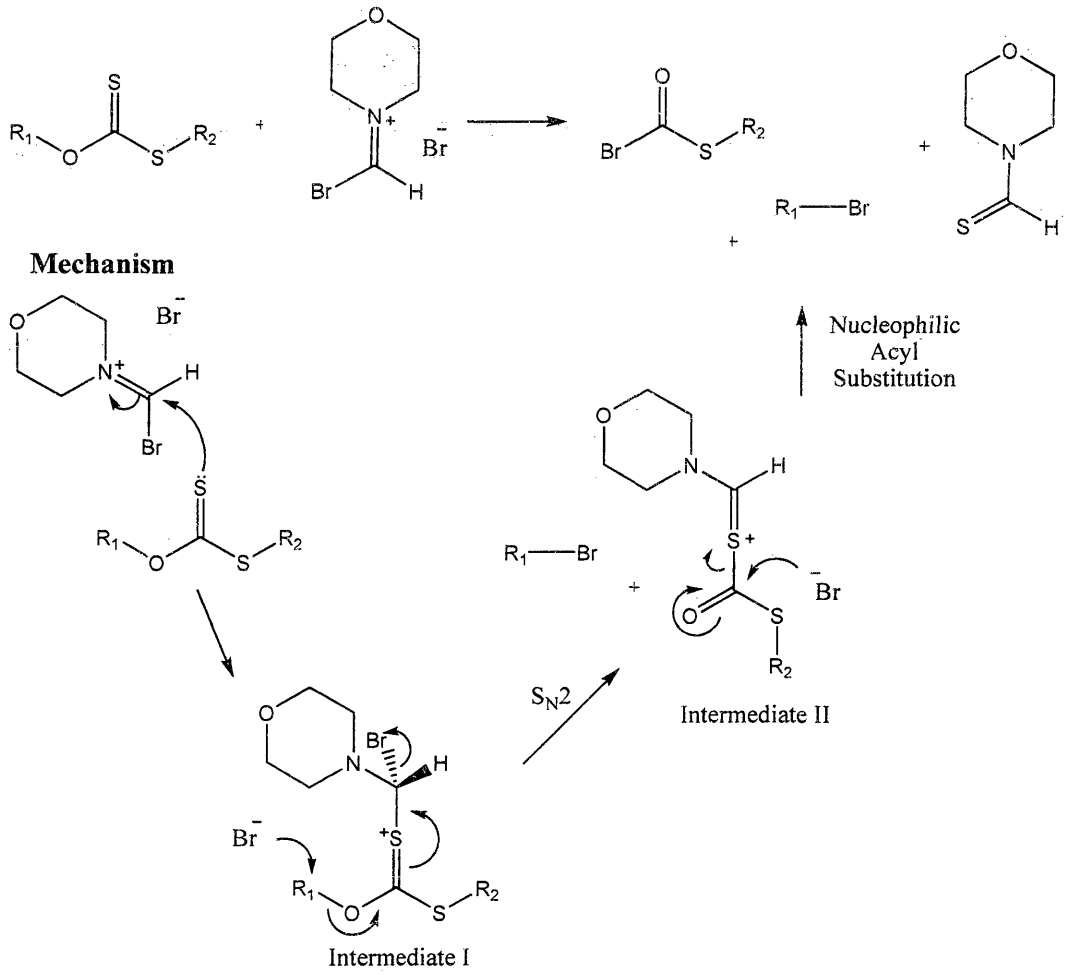
in an attempt to develop a new synthetic method. Subsequent work in our lab indicates that the Vilsmeier reagent works well for the transformation of dimethylcarbamate protected alcohols to the corresponding alkyl halide.[6]

Figure 2: Vilsmeier Transformation of Dimethylcarbamates[6]



Dimethylcarbamates, similar in structure to xanthates, are stronger nucleophiles which is a consequence of resonance electron donation provided by the dimethylamino group. This initial study provided sufficient yields to warrant further investigation into the reaction of the xanthate protected alcohol. Provided below in Figure 3 is the Vilsmeier transformation reaction for the bromination of a xanthate protected alcohol.

Figure 3: Vilsmeier Transformation of Xanthate Protected Alcohols

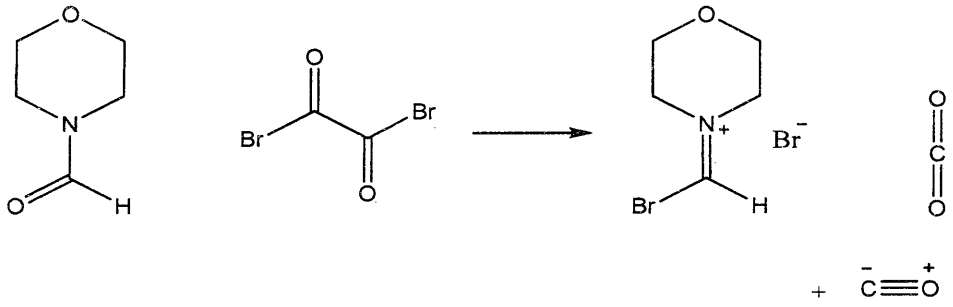


The mechanism, proposed in earlier work by our lab, involves an initial nucleophilic attack of the imine sp^2 carbon by the nucleophilic sulfur of the thiocarbonyl to form Intermediate I. In the next step an S_N2 mechanism occurs in which a nucleophilic bromide anion attacks the backside of the carbon alpha to the alcohol oxygen of the xanthate ester to form Intermediate II as well as the alkyl halide of the original alcohol. This reaction is concerted and coupled with the formation of a more stable carbonyl and the elimination of a bromide anion. In

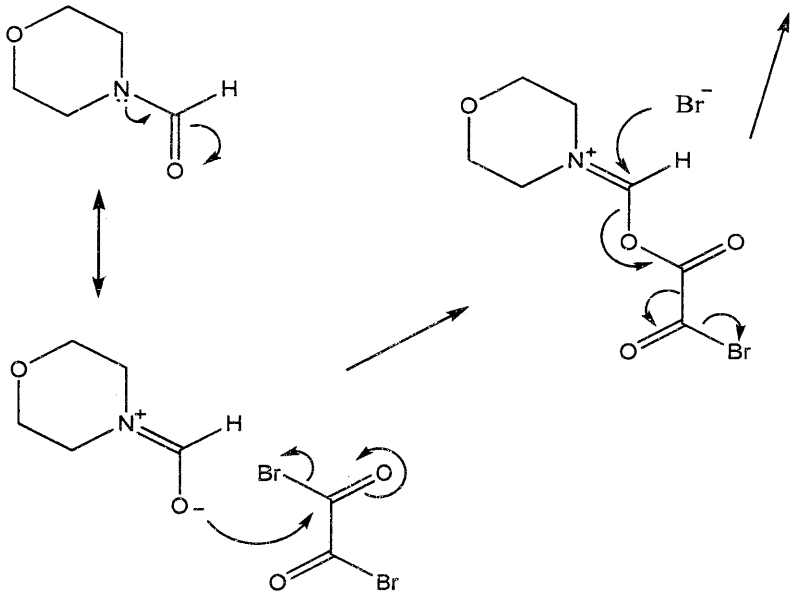
the final step, the displaced bromide anion acts as a nucleophile in an acyl substitution to produce *S*-alkyl bromothioformate and 4-thioformylmorpholine.

The preparation of the Vilsmeier reagent (Figure 4) involves the reaction for 4-formylmorpholine with oxalyl bromide. The mechanism, as shown below, involves two separate addition-elimination steps from which the reagent precipitates out of solution as a white solid and carbon dioxide and carbon monoxide evolve as gases.

Figure 4: Vilsmeier Reagent Synthesis via Oxalyl Bromide

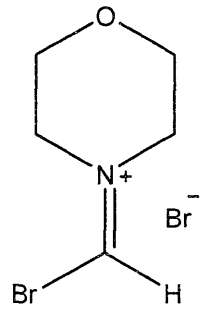


Mechanism



Experimental Procedures

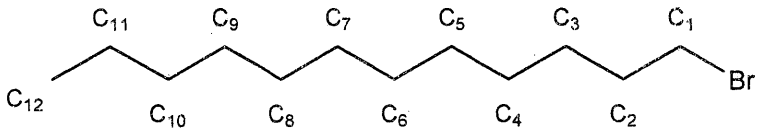
GC-MS characterizations were completed using an *Agilent Technologies Model 5973 Network Mass Selective Detector* (GC-MS system) coupled with *Hewlett-Packard* processing capabilities. ^{1}H-NMR and ^{13}C-NMR spectra were standardized to tetramethylsilane and chemical shifts were recorded in ppm and Hz. The data was obtained using a *Varian Mercury 400VX Model* (400 MHz) Cryogenic NMR with *Varian VNMR 6.1B* programming and *NUTS 1D* NMR data processing.



Vilsmeier Reagent

General Procedure for 15 mmol reaction: To a round bottom flask methylene chloride (25 mL) and 4-formyl-morpholine (1.50 mL) were added with stirring. The reaction flask was then cooled in an ice bath to 0 °C. Oxalyl bromide (1.40 mL) was then added dropwise using a syringe. The reaction releases a mixture of carbon dioxide and carbon monoxide so a well ventilated hood was used. The ice bath was then removed and the reaction was stirred vigorously for twenty minutes. Preparation of the Vilsmeier reagent was considered complete when a clean white salt remained in a colorless solvent. A yellow tint to the mixture was

an indication that un-reacted oxalyl bromide was present, and a few extra drops of 4-formyl-morpholine were then added to complete the reaction.



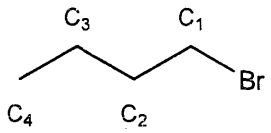
Xanthate I Transformation: 1-Bromododecane

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: The Vilsmeier reagent was prepared as described in the general procedure. Separately, 2.76 grams of **I** was dissolved in methylene chloride (10 mL) and added dropwise into the reaction flask containing the Vilsmeier reagent. GC-MS analysis after 4 hours indicated that the reaction was not complete so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the contents of the round bottom flask were gravity-filtered to remove remaining salts and the methylene chloride solvent was then removed via Rotovap. A yellowish-orange oil remained and was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was washed with acetonitrile (2 x 50 mL) and the solvent was removed again by Rotovap. A clear oil, 1-bromododecane, remained and was distilled under vacuum at 0.3 Torr with a boiling point of 81-82 °C. The percent conversion was calculated using GC-MS and determined to be 80% and the yield was 58%. Product identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figure A 53 and 55-57).

Experimental Procedure for 1.0 equivalent Vilsmeier Reagent: The procedure for the 1.0 equivalent Vilsmeier transformation was identical to the 1.5 equivalent reaction procedure except the volumes of 4-formyl-morpholine and oxalyl

bromide were 1.00 mL and 0.94 mL respectively. Samples were collected at 0.5, 1.0, 1.5, 2.0 and 96.0 hours and injected into the GC-MS for analysis. The percent conversions were determined to be 39%, 41%, 42%, 43%, and 54% respectively. Due to low conversion, yields were not determined.

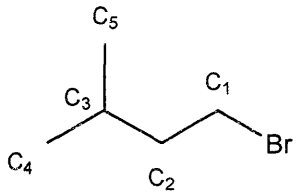
Experimental Procedure for 2.0 equivalents Vilsmeier Reagent: The procedure for the 2.0 equivalent Vilsmeier deprotection was identical to the 1.5 equivalent reaction procedure except the volumes of 4-formyl-morpholine and oxalyl bromide were 2.00 mL and 1.88 mL respectively. The percent conversion was calculated using GC-MS and found to be 98% and the yield was 67%. Product identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figure A 54-57).



Xanthate II Transformation: 1-Bromobutane

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: The Vilsmeier reagent was prepared as described in the general procedure. Separately, **II** (1.64 g) was dissolved in Methylene chloride (10 mL) and added dropwise into the reaction flask containing the Vilsmeier reagent. GC-MS analysis after 4 hours indicated that the reaction was not complete so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the contents of the round bottom flask were gravity-filtered to remove remaining salts and the methylene chloride solvent was then removed via fractional distillation at atmospheric pressure. A yellowish-orange oil remained un-distilled and was then

dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was washed twice with acetonitrile (50 mL each) and transferred back to the distillation apparatus. After a careful 4 hour fractional distillation a condensed solution of petroleum ether and 1-bromobutane was obtained. The percent conversion was determined to be 70% and the yield was not determined due to the volatility of 1-bromobutane, which made it difficult to isolate. Product identity was confirmed and percent conversion was calculated using GC-MS data (Figure A 58-59).

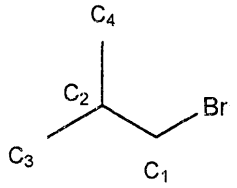


Xanthate III Transformation: 1-Bromo-3-methylbutane

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: The Vilsmeier reagent was prepared as described in the general procedure. Separately, **III** (1.78 g) was dissolved in methylene chloride (10 mL) and added dropwise into the reaction flask containing the Vilsmeier reagent. GC-MS analysis after 4 hours indicated that the reaction was incomplete so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the contents of the round bottom flask were gravity-filtered to remove remaining salts and the methylene chloride solvent was then removed via fractional distillation at atmospheric pressure. A yellowish-orange oil remained un-distilled and was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was washed twice with acetonitrile (50 mL each) and transfered back to

the distillation apparatus. After a careful 4 hour fractional distillation a condensed solution of petroleum ether and 1-Bromo-3-methylbutane was obtained. The percent conversion was determined to be 62% and the yield was not determined due to the volatility of 1-bromo-3-methylbutane. Product identity was confirmed and percent conversion was calculated using GC-MS data (Figure A 60 and Figure A 62).

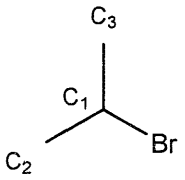
Experimental Procedure for 2.0 equivalents Vilsmeier Reagent: The procedure for the 2.0 equivalent Vilsmeier transformation was identical to the 1.5 equivalent reaction procedure except for the volumes of 4-formyl-morpholine and oxalyl bromide were 2.00 mL and 1.88 mL respectively. The percent conversion was calculated using GC-MS and found to be 90% and the yield was not determined. Product identity was confirmed and percent conversion was calculated using GC-MS data (Figures A 61-62).



Xanthate IV Transformation: 1-Bromo-2-methylpropane

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: The Vilsmeier reagent was prepared as described in the general procedure. Separately, **IV** (1.64 g) was dissolved in methylene chloride (10 mL) and added dropwise into the reaction flask containing the Vilsmeier reagent. GC-MS analysis after 4 hours indicated that the reaction was not complete so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the

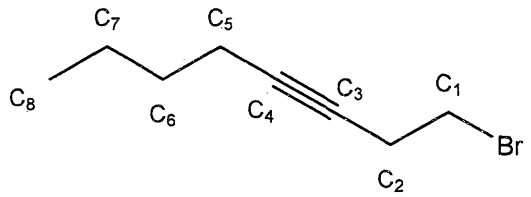
contents of the round bottom flask were gravity-filtered to remove remaining salts and the methylene chloride solvent was then removed via fractional distillation at atmospheric pressure. A yellowish-orange oil remained un-distilled and was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was washed twice with acetonitrile (50 mL each) and transferred back to the distillation apparatus. After a careful 4 hour fractional distillation a condensed solution of petroleum ether and 1-bromo-2-methylpropane was obtained. The percent conversion was determined to be 57% and the yield was not determined due to the volatility of 1-bromo-2-methylpropane. Product identity was confirmed and percent conversion was calculated using GC-MS data (Figures A 63-64).



Xanthate V Transformation: 1-Bromo-1-methylethane

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: The Vilsmeier reagent was prepared as described in the general procedure. Separately, **V** (1.64 g) was dissolved in methylene chloride (10 mL) and added dropwise into the reaction flask containing the Vilsmeier reagent. Immediately upon addition of the xanthate to the reaction flask the Vilsmeier salt dissolved completely. This was uncharacteristic in that all the previous reactions retained a large amount of unreacted reagent salt, which was separated later by way of gravity filtration. GC-MS analysis after 1 hour showed the reaction to be complete with no detectable amount of **V** present. However, the product 1-bromo-1-methylethane was also undetected. The reaction was confirmed by the appearance of the other products,

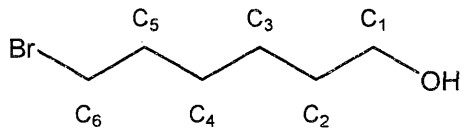
methyl bromothiolformate and 4-thioformylmorpholine which indicated conclusively that the reaction had occurred. The lack of detection of 1-bromo-1-methylethane was likely a result of the compound's volatility, resulting in co-elution with the solvent, which is not analyzed by the instrument. The percent conversion was determined to be greater than 99.9% and the yield was not determined. Percent conversion was calculated using GC-MS data (Figures A 65-67).



Xanthate VI Transformation: 1-Bromo-oct-3-yne

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: VI (2.16 g) was dissolved into methylene chloride (10 mL) in a round bottom flask with a magnetic stir bar. Separately, the Vilsmeier reagent was prepared as described in the general procedure. The reagent solution was then carefully transferred dropwise in to the stirring xanthate solution. GC-MS analysis after 4 hours indicated that the reaction was not complete so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours GC-MS analysis showed 1-bromo-oct-3-yne as the major product with little to no bromination at the triple bond. The contents of the round bottom flask were gravity filtered to remove remaining salts and the methylene chloride solvent was then removed via Rotovap. A yellowish-orange oil remained and was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This

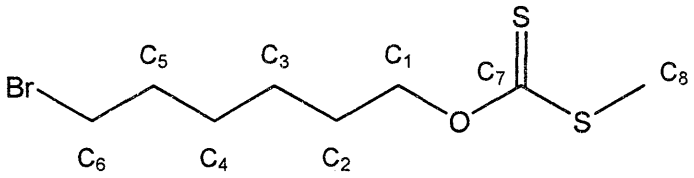
solution was washed with acetonitrile (2 x 50 mL) and transferred back to the Rotovap where the pet ether was removed. A clear oil remained and was analyzed via GC-MS analysis. Though 1-bromo-oct-3-yne was the major product there was significant bromination at the triple bond to give a mixture of products. The percent conversion was calculated using GC-MS data and determined to be 83% but the yield was undetermined, due to inability to separate the brominated derivatives. Product identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 68-73).



Xanthate VII Transformation: 6-Bromohexan-1-ol

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: VII (2.08 g) was dissolved into methylene chloride (10 mL) in a round bottom flask with a magnetic stir bar. Separately, the Vilsmeier reagent was prepared as described in the general procedure. The reagent solution was then carefully transferred dropwise in to the stirring xanthate solution. GC-MS analysis after 4 hours indicated that the all the reactant had been brominated at the hydroxyl group. It was also noted that the xanthate functionality remained largely conserved so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the contents of the round bottom flask were gravity filtered to remove remaining salts and the methylene chloride solvent was then removed via Rotovap. A yellowish-orange oil remained and was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was

washed twice with acetonitrile (50 mL each) and transferred back to the Rotovap where the petroleum ether was removed. A clear oil remained and GC-MS analysis showed a mixture of 11% 1,6-dibromohexane, 89% *O*-(6-bromohexyl)-*S*-methylxanthate, and a complete absence of both the initial substrate **VII** and the predicted product 6-bromohexan-1-ol. The percent conversion was determined to be greater than 99.9% and the yield was not determined. A sample of *O*-(6-bromohexyl)-*S*-methylxanthate was isolated via distillation under vacuum at 0.3 Torr with a boiling Point of 124-126 °C and a yield of 16.5%. No 1,6-dibromohexane was recovered. Product identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 74-78).

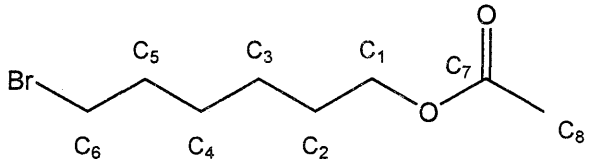


Xanthate VIII Transformation: *O*-(6-bromohexyl)-*S*-methylxanthate

10 mmol Experimental Procedure for 1.5 equivalents Vilsmeier Reagent:

VIII (2.98 g) was dissolved into methylene chloride (10 mL) in a round bottom flask with a magnetic stir bar. Separately, the Vilsmeier reagent was prepared as described in the general procedure above. The reagent solution was then carefully transferred dropwise in to the stirring xanthate solution. GC-MS analysis after 4 hours showed trace amounts of **VIII** so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the contents of the round bottom flask were gravity filtered to remove remaining salts and the methylene chloride solvent was then removed via Rotovap. A yellowish-orange oil remained and was then dissolved in petroleum ether (50 mL) and transferred to

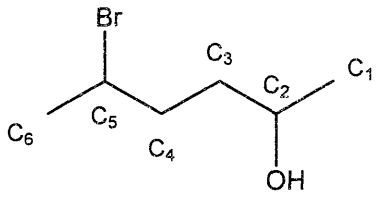
a separatory funnel. This solution was washed twice with acetonitrile (50 mL each) and transferred back to the Rotovap where the pet ether was removed. A clear oil remained and GC-MS analysis showed a mixture of 25% 1,6-dibromohexane and 75% *O*-(6-bromohexyl)-*S*-methylxanthate. The percent conversion was determined to be 93%. *O*-(6-bromohexyl)-*S*-methylxanthate was isolated via distillation under vacuum at 0.3 Torr with a boiling point of 124-126 ^{o}C and a yield of 46%. Product identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figure A 75-79).



Xanthate IX Transformation: 6-Bromohexyl acetate

10 mmol Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: IX (2.50 g) was dissolved into methylene chloride (10 mL) in a round bottom flask with a magnetic stir bar. Separately, the Vilsmeier reagent was prepared as described in the general procedure. The reagent solution was then carefully transferred dropwise in to the stirring xanthate solution. GC-MS analysis after 4 hours showed unreacted **IX** so the reaction was left stirring for 24 hours before workup to allow for maximal conversion. After 24 hours the contents of the round bottom flask were gravity filtered to remove remaining salts and the methylene chloride solvent was then removed via Rotovap. A yellowish-orange oil remained and was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was washed twice with acetonitrile (50 mL each) and

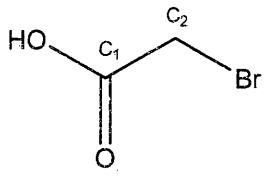
transfered back to the Rotovap where the pet ether was removed. A clear oil remained and GC-MS analysis showed a mixture of 6-bromohexyl acetate, **IX**, and a large amount of impurities and side products (Figure A 80). It should be noted that the starting sample of **IX** was relatively impure do to numerous isolation steps as well as the extended storage time before deprotection. The percent conversion was also determined to be 39% and 6-bromohexyl acetate was isolated via distillation under vacuum at 0.3 Torr with a boiling point of 124-126 ^{o}C and a yield of 8%. Product identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 80-83).



Xanthate X Transformation: 5-Bromohexan-2-ol

10 mmol Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: X (2.08 g) was dissolved into methylene chloride (10 mL) in a round bottom flask with a magnetic stir bar. Separately, the Vilsmeier reagent was prepared as described in the general procedure above and then carefully transferred dropwise in to the stirring xanthate solution. The Vilsmeier reagent dissolved immediately upon addition to the reaction flask, which was uncharacteristic in that all the previous reactions retained a large amount of unreacted reagent salt. GC-MS analysis after 1 hour showed the reaction to be complete with no detectable amount of **X** present. However, it was also noted that the xanthate functionality remained largely conserved. The methylene chloride solvent was removed via

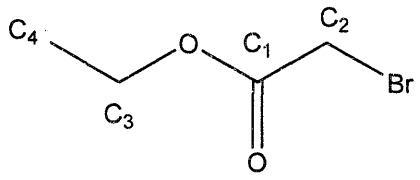
Rotovap, leaving a yellowish-orange oil that was then dissolved in petroleum ether (50 mL) and transferred to a separatory funnel. This solution was washed twice with acetonitrile (50 mL each) and transferred back to the Rotovap where the pet ether was removed. A clear oil remained and GC-MS analysis showed a mixture of 55% 2,5-dimbromohexane, 45% *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate, and a complete absence of the initial **X** and the anticipated product 5-bromohexan-2-ol. The percent conversion was determined to be greater that 99.9% and the yield of 5-bromohexan-2-ol was not dertermined. Samples of 2,5-dimbromohexane and *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate were isolated via distillation under vacuum at 0.3 Torr with boiling points of 51-52 °C and >70 °C and yields of 46% and 8% respectively. Both products were approximately equal mixtures of the diastereomers, based off of relative peak intensities for isomeric ^{13}C-NMR. Product identities were confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figures A 84-90).



Xanthate XI Transformation: 2-Bromoethanoic acid

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: XI (1.80 g) was dissolved into methylene chloride (10 mL) in a round bottom flask with a magnetic stir bar. Separately, the Vilsmeier reagent was prepared as described in the general procedure and then carefully transferred dropwise in to the stirring xanthate solution. GC-MS analysis after 4 hours showed that no **XI** remained. Additionally, there was a significant amount of ethyl bromothiolformate and 4-

thioformylmorpholine in the flask, which is clear evidence that the xanthate moiety reacted. However, the expected product, 2-bromoethoic acid, was not present in GC chromatograph. The product was believed to have precipitated out of the methylene chloride in the form of a salt. 20% sulfuric acid (50 mL) was added to the reaction flask. This quenched the excess Vilsmeier reagent and dissolved all other salts in the flask. A second GC-MS sample of the methylene chloride layer was run showing only a slight trace amount of 2-bromoethoic acid. In a final attempt to isolate the product, 2.0 grams of sodium chloride were added to the aqueous layer. A third GC-MS run showed no improvement in product extraction. Product yield was not determined, but identity was confirmed via GC-MS (Figures A 91-92).



Xanthate XII Transformation: Ethyl 2-Bromoethanoate

Experimental Procedure for 1.5 equivalents Vilsmeier Reagent: No reaction was completed due to time constraints and a lack of available **XII**. If the reaction had been run the procedure would have been identical to that of **XI**.

Chemeoselective Study of Vilsmeier Reagent on Substrates with Hydroxyl and Xanthate Functionalities

Experimental Procedure for 1.0 mmol Vilsmeier Reagent reacting with 2.0 mmol VII: The procedure for the synthesis of the Vilsmeier reagent was identical to the general procedure except the volumes of 4-formyl-morpholine and oxalyl bromide were 0.100 mL and 0.094 mL respectively. Separately, **VII** (0.42 g) was dissolved into methylene chloride(10 mL). The Vilsmeier reagent was then carefully transferred dropwise in to the stirring xanthate solution. GC analysis of the reaction pot after 2 hours shows a mixture of 97% *O*-(6-bromohexyl)-*S*-methylxanthate and 3% 1,6-dibromohexane (Figure A 93).

Experimental Procedure for 1.0 mmol Vilsmeier Reagent reacting with 2.0 mmol X: The procedure for the synthesis of the Vilsmeier reagent was identical to the general procedure above except the volumes of 4-formyl-morpholine and oxalyl bromide were 0.100 mL and 0.094 mL respectively. Separately, **X** (0.42 g) was dissolved into methylene chloride (10 mL). The Vilsmeier reagent was then carefully transferred dropwise in to the stirring xanthate solution. GC analysis of the reaction pot after 2 hours shows a mixture of 95% *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate and 5% 2,5-dimbromohexane (Figure A 94).

Results and Discussion

Table 1: Results of Xanthate Transformation

Xanthate	Vilsmeier Equivalent	Time (hrs)	% Yield	% Conversion[a]	Other Products
I	1.0	96	-	54	
I	1.5	24	58	80	
I	2.0	24	67	98	
II	1.5	24	0[a]	70	
III	1.5	24	0[a]	62	
III	2.0	24	0[a]	90	
IV	1.5	24	0[a]	57	
V	1.5	1	0[a]	>99.9	
VI	1.5	24	0	83	
VII	1.5	24	0	>99.9[b]	1,6-dimbromo-hexane, *O*-(6-bromohexyl)-*S*-methylxanthate
VIII	1.5	24	46	93	1,6-dimbromohexane
IX	1.5	24	8	39	
X	1.5	1	0	>99.9[b]	2,5-dimbromohexane, *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate
XI	1.5	2	0	>99.9	
XII	-	-	-	-	

[a]Product too volatile to isolate, [b]Alcohol selectively brominated before Xanthate was deprotected

Given the yield results above in Table 1, it may appear that the Vilsmeier transformation is an inadequate method for xanthates. This, however, is not the case. The majority of the poor yields are primarily a result of using small alcohol substrates that are nonvolatile when protected but extremely volatile when reacted to form the subsequent bromoalkane. As a consequence these products proved to be difficult to isolate from solvents. Additionally, the larger xanthates (**VII** and **X**) that show yields of 0% actually reacted to produce unexpected products due to the chemeoselective preferences of the Vilsmeier reagent. Fortunately, the ability to collect percent conversion data through GC-MS analysis allowed for a wealth of information to be gathered.

Protected 1° Alcohols with no other functional groups (I, II, III and IV)

Recently we reported that thiocarbamate protected alcohols (1°) are converted to the cooresponding alkyl halides by treatment with 1.5 equivalents of Vilsmeier reagent to give high rates of conversion and good yields.[6] The reactions in this study like those were also carried out with 1.5 equivalents of Vilsmeier reagent. For compounds (**I- IV**) it was determined that 1.5 equivalents of the Vilsmeier reagent was not completely effective at removing the xanthate moiety. This was expected because thiocarbamates are generally better nucleophiles than xanthates.[6] Increasing the amount of reagent to 2.0 equivalents (**I** and **III**) significantly enhanced the efficacy of the Vilsmeier reagent – elevating the conversion from 80% to 98% for **I** and from 62% to 90% for **III**. These results indicate that lower yields can be corrected by simply increasing the amount of reagent.

The results also reveal that branching in the proximal region of the protected hydroxyl decreases the efficacy of the reagent. The percent conversions for the 1.5 equivalent reactions for **II**, **III**, and **IV** follow the pattern **II** > **III** > **IV**, where **II** is a straight chain butyl, **III** has a methyl at the gamma position and **IV** has a methyl at the beta position. This result is consistent with an S_N2 type mechanism where increased branching near the site of displacement hinders reactivity. It should also be noted that increasing the equivalent amount of reagent does, in the case of **III**, enhance yields. Excessive steric hindrance, however, may prove to be problematic.

Another note to make about the Vilsmeier conversion of xanthate protected 1° alcohols is that the reaction time necessary for complete conversion is relatively long. Initially, we believed that the reagent was quenched due to atmospheric contamination. However, the data in Table 2 below is from a 1.0 equivalent Vilsmeier reaction and indicates that the reaction may persist for long periods of time.

Table 2: Transformation of I with 1.0 equivalent Vilsmeier Reagent

Elapsed Time (hrs)	% Conversion (1-Bromo-dodecane)
0.5	39
1.0	41
1.5	42
2.0	43
24.0	50
96.0	54

This reaction was loosely capped and not carried out under nitrogen, which indicates that reagent quenching due to atmospheric contamination, may not be an issue. Nevertheless, given the propensity for xanthates to be oxidized to their thiocarbonyl derivatives after prolonged exposure to the atmosphere, it would be advisable to carry out the Vilsmeier transformation reactions in an inert gaseous environment (nitrogen or argon).[7]

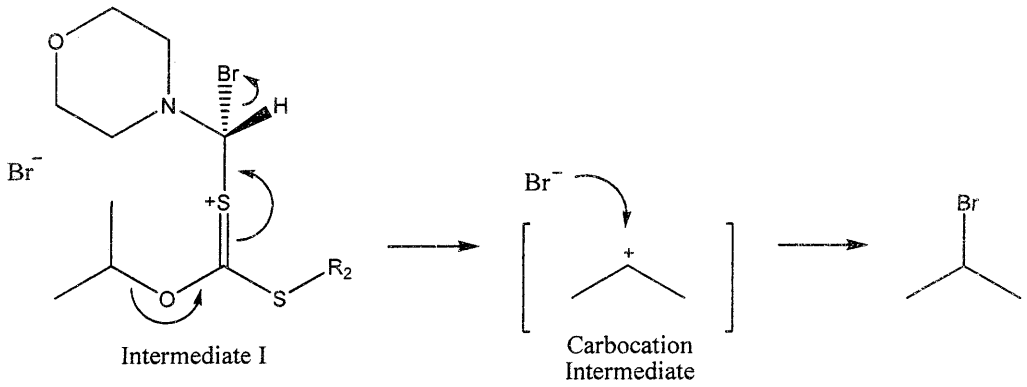
Protected Secondary Alcohols with no other functional groups (V)

An unexpected and interesting result came out of the transformation of **V**. Given the previously discussed pattern of steric interference and the fact that the methyl in **V** is alpha to protected oxygen, it was expected that the percent conversion would be even lower than that of **IV**. However, the reagent salt essentially dissolved when the xanthate solution was added. Additionaly, GC

analysis showed the reaction to be complete with > 99.9 % conversion in less than an hour.

One possible explanation for the observed change in reactivity is that the second phase of the transformation (mechanism shown in Figure 1) has changed from an S_N2 type displacement to an S_N1 type mechanism. Shown below in Figure 8 is the proposed mechanism for **V**.

Figure 5: S_N1 Mechanism Proposed for the deprotection /transformation of V

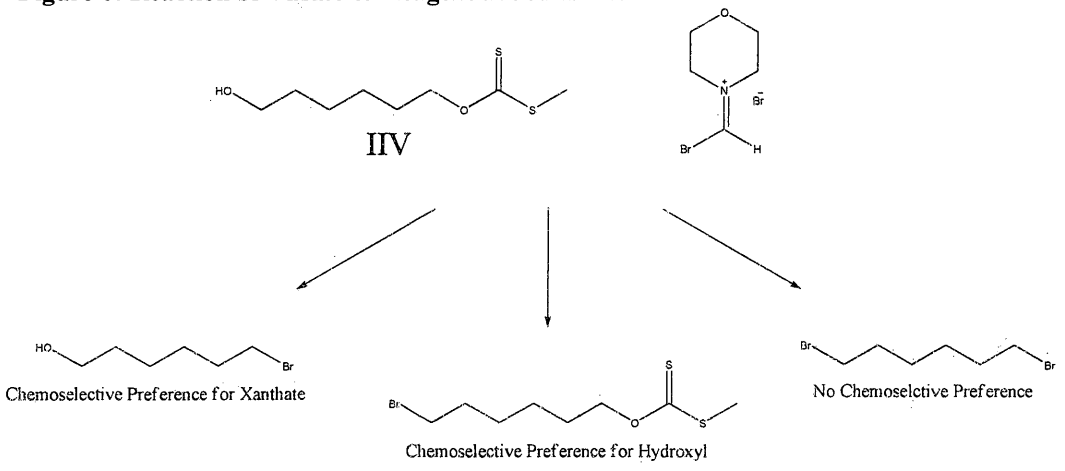


In this mechanism Intermediate I still decomposes to form Intermediate II, however rather than producing a bromoalkane in the process a 2° carbocation intermediate of the initial alcohol is formed. The carbocation then reacts with nucleophillic bromide to give the bromoalkane product. This proposed mechanism is probable because of the inherent stability of the secondary carbocations. Such stability would result in a greatly reduced activation energy and a quicker reaction, which is consistent with the experimentally observed results. **X**, another xanthate protected 2° alcohol (discussed later) gave similar results.

Multiple Functional Groups Present (VI-XI)

Compounds **VI – XI** contained both the xanthate moiety as well as one other functional group. In these cases, when multiple functionalities are present, the potential exists for the different groups to compete for a limited amount of Vilsmeier reagent. As a result the deprotection procedure was modified in order to observe any chemoselective preference for the Vilsmeier reagent. This was accomplished by slowly adding 1.5 equivalents of the Vilsmeier reagent to the xanthate solution. Given that each xanthate molecule had 2 functional groups, the reagent was limiting and any selectively favored functionality reacted preferentially. Subsequent analysis of the products showed whether or not there was a preference. A truly correct test for chemoselectivity would use only 1.0 equivalent of Vilsmeier reagent. However, since earlier reactions had shown that the reagent was not completely effective at removing the xanthate moiety, the reaction ratios were maintained at 1.5 equivalents reagent to 1.0 equivalent substrate in hopes of obtaining better yields for product analysis. Compounds **VI-XI** where all reacted in this manner. Shown below is a hypothetical depiction of the experiment for **VII**.

Figure 6: Reaction of Vilsmeier Reagent added to VII



The results from these experiments were very interesting. Compound **VI** contained an alkyne triple bond as well as a xanthate group. The transformation was similar to the deprotection of **I**, with 83 % conversion. There was also a considerable amount of bromination at the triple bond, producing the side-products 1,3-dibromo-oct-3-ene and 1,4-dibromo-oct-3-ene. This however, was ruled out as a competitive reaction because the initial GC-MS analysis of the reaction pot, before the workup procedure, showed only marginal bromination at the triple bond. Further work is necessary to determine if a proper workup procedure can be created that will conserve the alkyne functionality.

VII and **X** both contained a hydroxyl group as well as a xanthate group. After initial GC-MS analysis, it quickly became evident that the reactions were competitive and favored the bromination of the hydroxyl group over the transformation of the xanthate. This was determined from the fact that for both compounds the hydroxyl groups reacted at > 99.9 % conversion and the xanthates reacted at 11% and 55% for **VII** and **X** respectively. An additional element of complexity was the fact that **X** was also a protected secondary alcohol and, like **V**, expressed a higher level of reactivity than **VII**, a primary protected alcohol.

Two questions arose from these results. First, how much more selective is the reagent for the hydroxyl than the xanthate group? And second, is the increased xanthate reactivity of **X** attributable to the proposed S_N1 mechanism discussed for **V**? To answer these questions an addition small scale reaction was run for **VII** and **X** to determine the absolute chemeoselective preference of the reagent for

each. In these reactions 1 mmol of Vilsmeier reagent was added dropwise to a stirring solution containing 2 mmol of the xanthate. This method made 4 functional groups available for every 1 reagent molecule.

Table 3: Results of Chemoselctive Study of VII and X

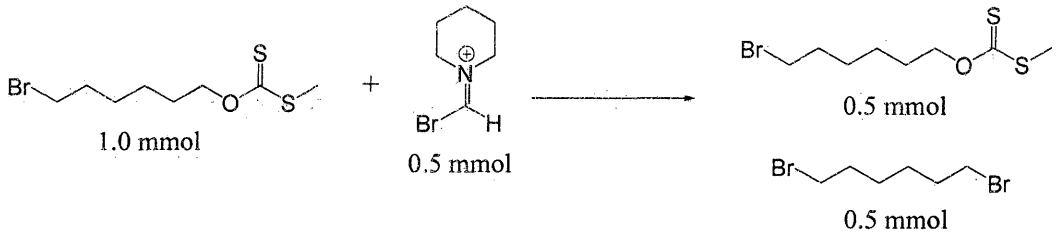
Xanthate	% Bromo-Xanthate Product	% Dibromo Product
VII	97	3
X	95	5

The results in Table 3 clearly indicate that there is a very strong chemeoselective preference for the hydroxyl group over the xanthate moiety for both **VII** and **X**. Additionally, both **VII** and **X** express approximately identical levels of selectivity. This information is not only important in itself, but it also allows us to re-evaluate the original reaction to show the relative reactivities of the two xanthates and help to infer whether or not **X** follows a similar mechanism to **V**. To do this the original reaction must be considered in the context of two separate reactions: one in which all the hydroxyl groups are brominated with 1.0 equivalent Vilsmeier reagent and the other in which the remaining 0.5 equivalents of Vilsmeier reagent react with the xanthate. In other words, if 15 mmol of Vilsmeier reagent was added to the reaction flask, 10 mmol will be consumed immeadiately via bromination of the hydroxyl group. The remaining 5 mmol would then be left to react with 10 mmol of xanthate.

Given this interpretation, it is reasonable then to make a correction so that the percent conversion only accounts for the transformation of the xanthate moiety. For example, the reaction for **VII** may now be considered as a

transformation of *O*-(6-bromohexyl)-*S*-methylxanthate with 0.5 equivalents of Vilsmeier reagent (Figure 10).

Figure 7



100% conversion would then result in a 50:50 mixture of 1,6-dimbromohexane and unreacted *O*-(6-bromohexyl)-*S*-methylxanthate. Similarly, the exact same approximation can be applied to **X**. The corrected conversion results are shown below in Table 4.

Table 4: Corrected % Conversions Excluding Hydroxyl Bromination

Xanthate	% Unreacted Bromo-Xanthate	% Dibromo Product	Corrected % Conversion
VII	89	11	22
X	45	55	110

Although the corrected value for **X** is unrealistically high, it is apparent that there is a significant difference in the relative reactivities. This, I believe, is a direct result of the fact that **X** is a 2° alcohol, and, like **V** it follows an S_N1 reaction mechanism.

Compound **VIII** was a fascinating molecule to study because it contains two xanthate functionalities. This is particularly important in terms of synthetic applications because the reaction will indicate whether or not the Vilsmeier Reagent will selectively remove a single xanthate functionality from a substrate containing multiple protected alcohols. Otherwise, the reagent would simply deprotect indiscriminately until all reagent and/or substrate has reacted completely. GC-MS analysis from the experiment showed that 93% of **VIII** reacted to give a mixture of 25% dibromoalkane (both ends deprotected) and 75% bromoalkylxanthate (one end deprotected). These results present a substantial argument in favor of the idea that the reagent selectively removes only one xanthate. However, it should also be noted that the conversion was not complete, and that a significant amount of the second xanthate functionality was removed to give the dibromoalkane. This means that the method of simply increasing to amount of Vilsmeier reagent to obtain better conversions will likely come at the expense of large amounts of the desired bromoalkylxanthate product. To better understand this reaction it would be ideal to run another reaction with 1.0 equivalent Vilsmeier reagent, which would allow us to determine whether or not the reagent is truly selective.

Xanthate **IX** is unique in that one end was esterified with acetate and the other end was esterified with *S*-methyldithiocarbonate (xanthate). Reacting **IX** with the Vilsmeier reagent provided an interesting insight into the relative reactivity of the carbonyl and the thiocarbonyl. The results from the experiment showed that the carbonyl displayed no apparent reactivity, while the xanthate, as

expected, was removed. The percent conversion was 39% and yield was 8% which were surprisingly low. However, given that the acetyl group expressed no reactivity, increasing the amount of reagent used could provide a simple solution.

XI is a xanthate protected form of glycolic acid. This compound, though a protected primary alcohol expressed a surprisingly high level of reactivity. Similar to the secondary alcohols, **XI** reacted to remove the xanthate functionality at >99.9%. However, the proposed S_N1 mechanism is unlikely due to the high instability of the carbocation intermediate that would result from such a mechanism. A more likely explanation is that the adjacent carboxyl group enhances the stabilization of the S_N2 reaction. This is supported by both experimental and theoretical studies that show elevated levels of reactivity for the carbon alpha to a carbonyl.[8] Lastly, it should be noted that the isolation of the product for this reaction proved to be extremely difficult and further work is needed to provide accurate yield results.

The Vilsmeier Reagent and Thiocarbonates

An interesting finding that became apparent after many deprotection reactions was that the oxidized xanthate derivatives, *O,S*-dialkylthiocarbonates, do not react with the Vilsmeier reagent. This is likely due to the fact that the *O,S*-dialkylthiocarbonate contains a carbonyl which is much less nucleophilic than the thiocarbonyl of a xanthate. Consequently, it is important to take extra care to

avoid oxidative conditions when carrying out the Vilsmeier transformation reactions.

Future Work

The Vilsmeier reagent works well for the transformation of a wide range of xanthate protected alcohols. Although the research reported here is preliminary there is considerable promise for future work in the project. Currently the major challenge in the project is to determine the mechanism for protected 2^{o} alcohols and determine how, if necessary, it can be controlled. If it the mechanism is confirmed as S_N1, then it is necessary to test different conditions to determine if the S_N2 mechanism can be selected. Instances of modifying the reaction conditions, such as solvent polarity and temperature, have been shown to drastically affect mechanisms in similar halide displacement reactions.[1] If conditions can be modified to produce a highly pure chiral product, then the method would be much more useful in complex syntheses. However, if the activation barrier for the S_N2 mechanism is simply too high to be overcome with reaction condition manipulation then it is still possible that modification of the xanthate *S*-alkyl group could also make a difference. Adding electron donating or withdrawing groups could be employed as a means to make the xanthate more reactive and effectively reduce the activation barrier of the S_N2 mechanism. Regardless of the outcome, the Vilsmeier reagent transformation is a useful new method for producing the alkyl halides from xanthate protected alcohols.

[1] Schlama, T.; Gouverneur, V.; Mioskowski, C. **One-step conversion of protected alcohols into alkyl halides using dimethylphosgeniminium salt.** Tetrahedron Letters (1997), 38(20), 3517-3520.

[2] Paquette, Leo A.; Fischer, John W.; Browne, Alan R.; Doecke, Christopher W. **Synthesis of [4] peristylane and functionalized derivatives of this hemispherical ring system.** Journal of the American Chemical Society (1985), 107(3), 686-91.

[3] Cristol, Stanley J.; Seapy, Dave G.. **New procedure for the transformation of alcohols to alkyl halides via xanthate esters and free-radical intermediates.** Journal of Organic Chemistry (1982), 47(1), 132-6.

[4] Barton, Derek H. R.; Stick, Robert V.; Subramanian, Raman. **Some reactions of soft electrophiles with esters and other compounds containing the thiocarbonyl group.** Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1976), (19), 2112-16.

[5] Gade, Alexandra M.; Abelt, Christopher J. **S-alkyl chlorothioformates from xanthates.** Synthesis (2007), (14), 2097-2099.

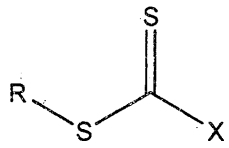
[6] Moynihan, Meagan F.; Tucker, Joseph F.; Abelt, Christopher J. **Alkyl bromides from dimethylthiocarbonates.** Tetrahedron Letters (Not Published Yet)

[7] See Chapter 3 on Oxidation

[8] Gineityte, V.. **On the origin of the enhanced reactivity of a -halocarbonyl compounds in SN2 processes.** THEOCHEM (2003), 663 47-58.

Chapter 5

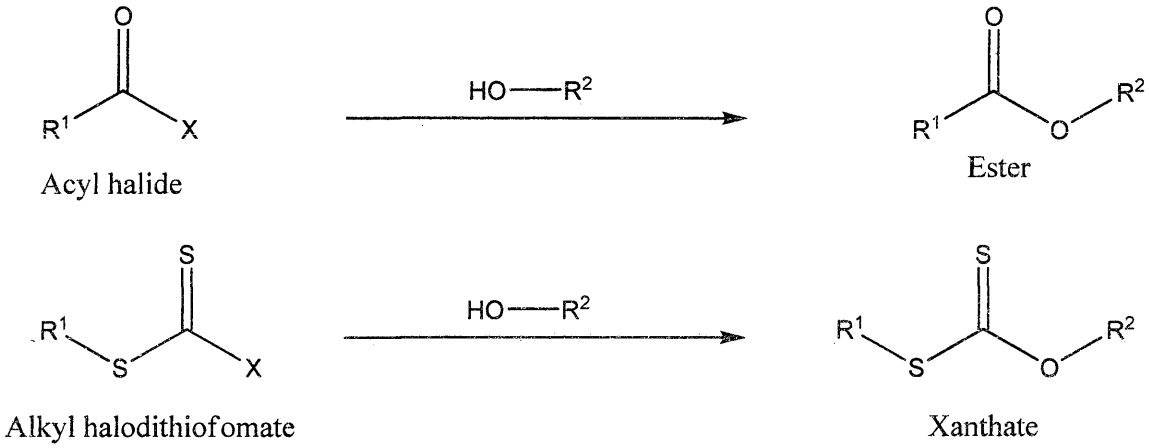
An Experimental Study of Alkyl Halodithioformates



Alkyl halodithioformates and Single-Step Xanthate Protection

Alkyl halodithioformates have a strikingly close chemical similarity to acyl halides, which have been shown to be useful as a selective reagent in the acetylation of hydroxyl groups.[1, 2] Given this similarity, it is reasonable to predict that alkyl halodithioformates can potentially react to make xanthates. This property is of particular importance to our project because it would provide a simple one-step synthetic method for producing xanthate protected alcohols.

Figure 1: Acylation Reactions of Acyl Halides and Alkyl Halodithioformates



Currently, studies have reported moderate yields (≤ 50%) for acylation reactions using alkyl chlorodithioformates in xanthate synthesis.[3, 4, 5] However, these yields are not practical in comparison to the more conventional methods of xanthate synthesis. One way to improve the yields is to produce a more reactive compound. Logically the bromide derivative would be more reactive because bromine is a better leaving group than chlorine. This thought is also supported experimentally by the fact that acyl bromides are

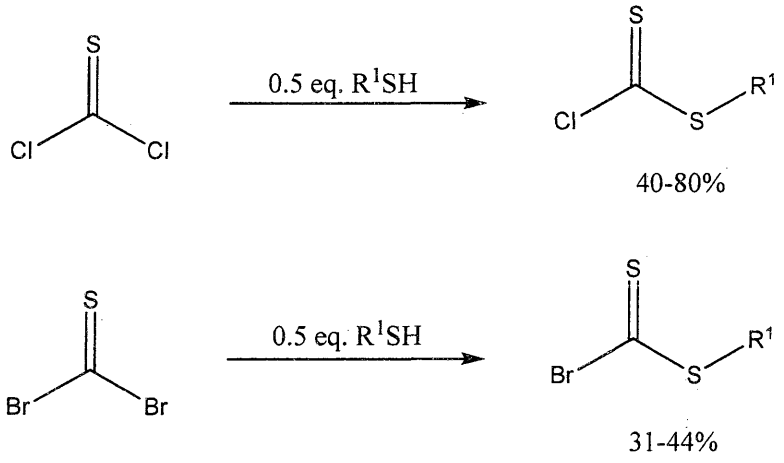
known to be more reactive that than acyl chlorides.[6] However, there have yet to be any reported studies on the bromo or iododithioformates to determine whether they are effective as xanthate precursors.

In this study we worked to develop simple a procedure for the general synthesis of alkyl bromodithioformates. The target molecule and focus of the study was methyl bromodithioformate, which was chosen because the *S*-methylxanthate ester is a simple and ideally small protective group.

Synthetic Methods

In 1937, Jensen first reported on the synthesis of alkyl chlorodithioformates.[7] This method involves a carefully controlled acylation reaction of 1 equivalent of thiophosgene with 0.5 equivalents of alkylthiol. Later, work with thiocarbonyl dibromide (the bromine analog of thiophosgene) showed similar results with slightly reduced yields.[8]

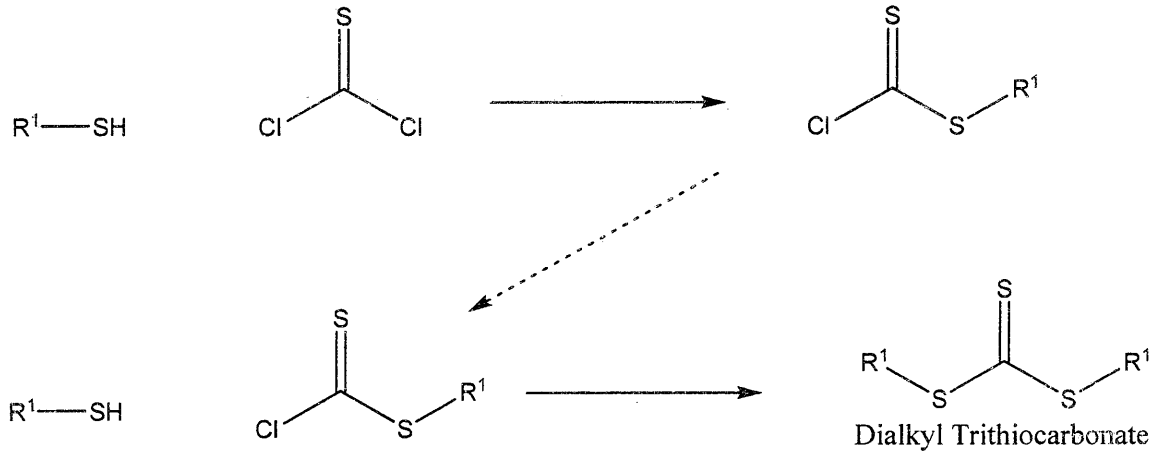
Figure 2: Jensen Synthetic methods[8]



Since the publication of Jensen's procedure very little progress has been made in the development of new synthetic methods.[8] Moreover, the new methods that have been reported fail to measure up in terms of procedural ease and/or product yield.[8]

There are, however, inherent problems in the Jensen procedure. Even with tightly controlled stoichiometric ratios, the production of the dialkyl trithiocarbonate byproduct is still reported.[2] From a purely mechanistic approach it is unlikely that this challenge will be overcome, because the alkyl chlorodithioformate product is reactive enough to compete for the alkylthiol reactant.

Figure 3: Proposed Mechanism for Production of Dialkyl Trithiocarbonate Byproduct

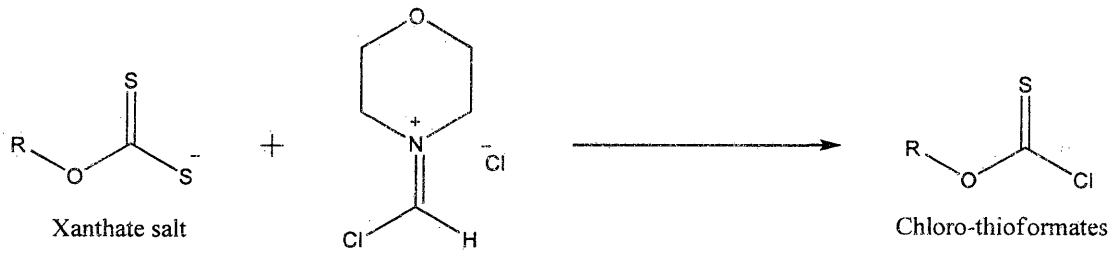


Our challenge was to develop a controlled method to produce the reactive product in a way such that the reactants are not consumed by the product, which is especially important if the bromodithioformate is more reactive than its chlorine.

Method Development

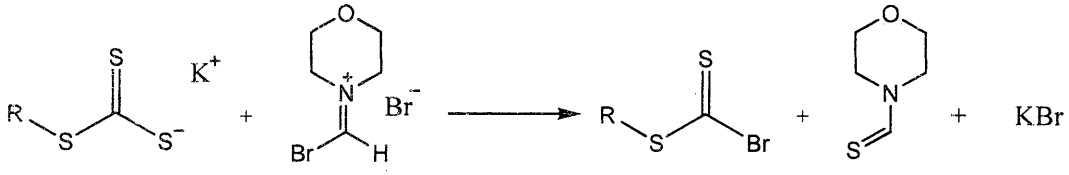
Past work in the Abelt lab has demonstrated that alkyl chlorothioformates can be synthesized in good yields by treating xanthate salts with the Vilsmeier reagent derived from 4-formylmorpholine.[9]

Figure 4: Synthesis of Alkyl Chlorothioformates from Xanthates

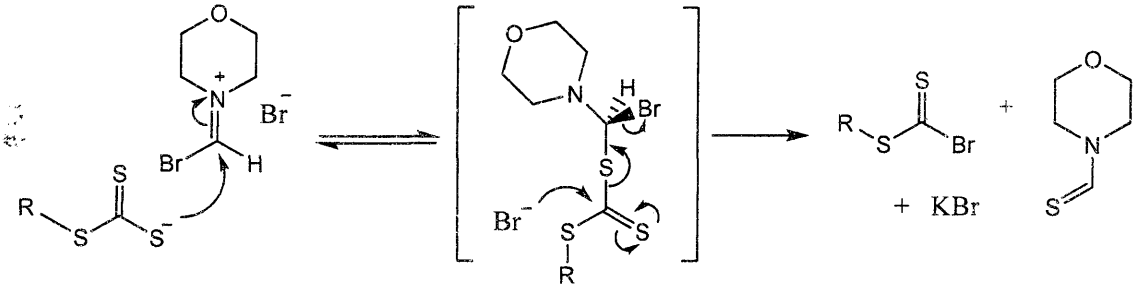


It is reasonable to then predict that the same reaction with a methyl trithiocarbonate salt should react similarly. The proposed reaction and mechanism is presented below in Figure 5.

Figure 5: Synthesis of Methyl Bromothioformate from Methyl Trithiocarbonate Salt



Mechanism



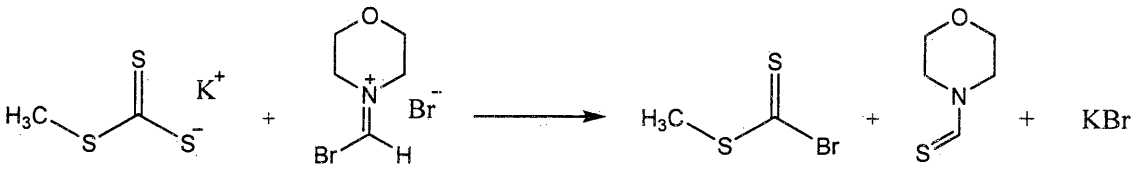
Synthetic Method

For the synthesis of methyl bromodithioformate, sodium methylthiolate is treated with carbon disulfide to give sodium methyl trithiocarbonate salt. The salt is then reacted with the Vilsmeier reagent to give methyl bromodithioformate. The proposed procedure is presented in Figure 6.

Figure 6: Proposed Synthesis of Methyl Bromodithioformate

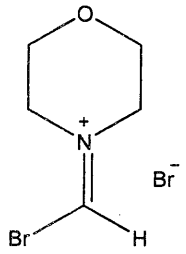
Step1

Step 2



Experimental

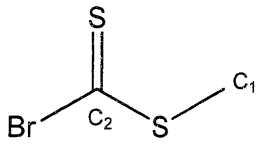
GC-MS characterizations were completed using an *Agilent Technologies Model 5973 Network Mass Selective Detector* (GC-MS system) coupled with *Hewlett-Packard* processing capabilities. ^{1}H-NMR and ^{13}C-NMR spectra were standardized to tetramethylsilane and chemical shifts were recorded in ppm and Hz. The data was obtained using a *Varian Mercury 400VX Model* (400 MHz) Cryogenic NMR with *Varian VNMR 6.1B* programming and *NUTS 1D* NMR data processing.



Vilsmeier Reagent

General Procedure for 30 mmol reaction: To a round bottom flask acetonitrile (35 mL) and 4-formylmorpholine (3.00 mL) were added with stirring. The reaction flask was then cooled in an ice bath to 0 °C. Oxalyl bromide (2.80 mL) was then added dropwise using a syringe. The reaction releases a mixture of carbon dioxide and carbon monoxide, so a well ventilated hood was used. The ice bath was then removed and the reaction was

stirred vigorously for 20 minutes. Preparation of the Vilsmeier reagent was considered complete when a clean white salt remained in a colorless solvent. A yellow tint to the mixture was an indication that unreacted oxalyl bromide was present, and a few extra drops of 4-formylmorpholine were then added to complete the reaction.

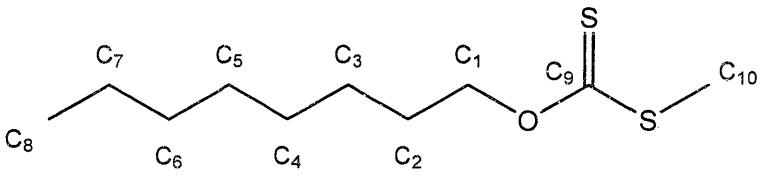


Methyl Bromodithioformate

Experimental Procedure for 20 mmol Reaction: Sodium thiomethoxide (1.40 g) was added to a round bottom flask. Acetonitrile (25 mL) was added to the flask and the mixture was stirred while adding carbon disulfide (1.23 mL) dropwise. Upon addition of carbon disulfide, the white thiomethoxide salt is consumed to give a yellow sodium methyl trithiocarbanate salt. This solution was stirred for approximately 1 hour. Separately, prepare the Vilsmeier reagent at a 30 mmol scale via the general procedure. To the flask containing the Vilsmeier reagent, carefully add the sodium methyl trithiocarbanate dropwise and slowly. After 6 hours of stirring the solution was light orange and the reaction was confirmed complete via GC-MS analysis. The compounds detected included methyl chlorodithioformate, methyl bromodithioformate, 4-formylmorpholine, dimethyl trithiocarbonate, and 4-thioformylmorpholine. To isolate the product, the contents of the flask were transferred to a separatory funnel and extracted 5 times with petroleum ether, 50 mL each. The petroleum ether was then removed via an aspirator vaccum leaving a red solution. Fractional distillation under 0.3 Torr gave methyl bromodithioformate as a yellowish-orange liquid with a boiling point of 58-80 °C.

The yield was 29% with a purity of 98%. Methyl chlorodithioformate was identified as the impurity. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figure A 95-100).

Failed Experimental Procedure: The procedure is identical to that directly above with the exception that the Vilsmeier reagent is added drop-wise to a stirring solution of the methyl trithiocarbanate salt. After 6 hours of stirring the solution was a deep crimson red. GC-MS analysis showed dimethyl trithiocarbanate as the primary product. A small sample of the reaction solution was also taken for a ^{13}C-NMR experiment which showed the presence of dimethyl trithiocarbanate and a possible peak for *bis*(methylthiothiocarbonyl)sulfane as well (Figure A 101). With no methyl bromodithioformate present the reaction was abandoned and yields were not determined. Also see Figures A 102-103.



***O*-octyl-*S*-methylxanthate**

Experimental Procedure for 10 mmol Reaction: Methyl bromodithioformate (1.72 g), octanol (2.60 g), and pyridine (1.58 g) added to a round bottom flask with stirring. After 2 hours GC-MS analysis indicated that no reaction had occurred. The flask was heated to 60 °C and sodium carbonate (2.00 g) was added. After approximately 24 hours GC-MS analysis showed no methyl bromodithioformate and large amount of *O*-octyl-*S*-methylxanthate was present. The contents of the reaction flask were transferred to a separatory funnel and dissolved into 25 ml petroleum ether (25 mL). This solution was then washed five times with H_2O (50 mL each), dried with sodium sulfate, and condensed

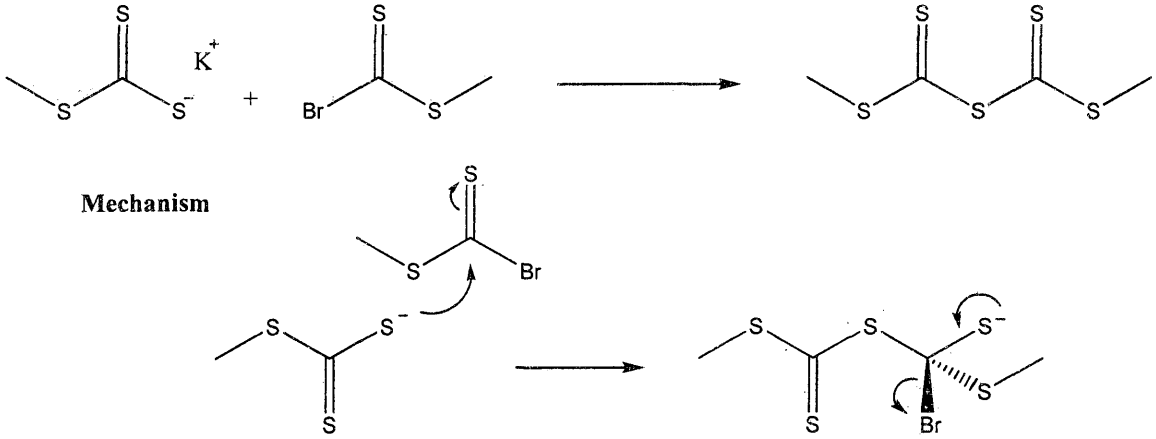
in vacuo on a Rotovap. The resulting yellowish-orange liquid was distilled at 0.3 Torr to give *O*-octyl-*S*-methylxanthate with a boiling point >75 °C and a yield of 17%. Compound identity was confirmed via ^{1}H-NMR, ^{13}C-NMR, and GC-MS (Figure A 104-106).

Results and Discussion

The synthetic method for methyl bromodithioformate proved to be very effective. The procedure is very simple and generates methyl bromodithioformate in both moderate yields and high purity. Furthermore, a small scale, 5 mmol, reaction with the chloro-Vilsmeier reagent demonstrated an identical level of reactivity. Thus, it is likely that this method has broad applicability for the general synthesis of alkyl bromo and chlorodithoformates.

There are, however, a few challenges to overcome concerning the synthetic reaction. Similar to Jensen's procedure, I believe the product is reactive enough to compete with the Vilsmeier reagent for the methyl trithiocarbonate reactant, producing *bis*(methylthiothiocarbonyl)sulfane.

Figure 6: Proposed Side Reaction

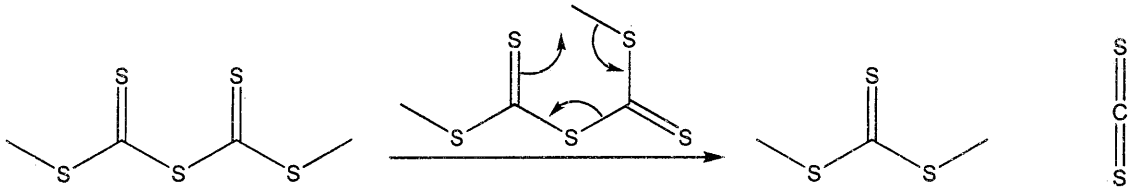


It is, however, difficult to determine that this side reaction actually occurs because there has yet to be any conclusive detection of *bis*(methylthiothiocarbonyl)sulfane using the instrumentation we have. GC-MS and NMR detection methods continually show dimethyl trithiocarbonate as the major side product. There is, however, a compelling study by Knoth and Gattow, in which they synthesized *bis*(methylthiothiocarbonyl)sulfane by reacting methyl chlorodithoformate with methyl trithiocarbonate salt.[10]

Figure 7: Synthesis of *bis*(methylthiothiocarbonyl)sulfane[10]

The conditions for the Knoth and Gattow reaction are identical to those in the procedure for the synthesis of methyl bromodithoformate. Moreover, Knoth and Gattow report that *bis*(methylthiothiocarbonyl)sulfane decomposed in their GC-MS instrument to give dimethyl trithiocarbonate.[10] I believe that *bis*(methylthiothiocarbonyl)sulfane may actually be less stable than they reported. Provided below is a likely mechanism for the decomposition reaction.

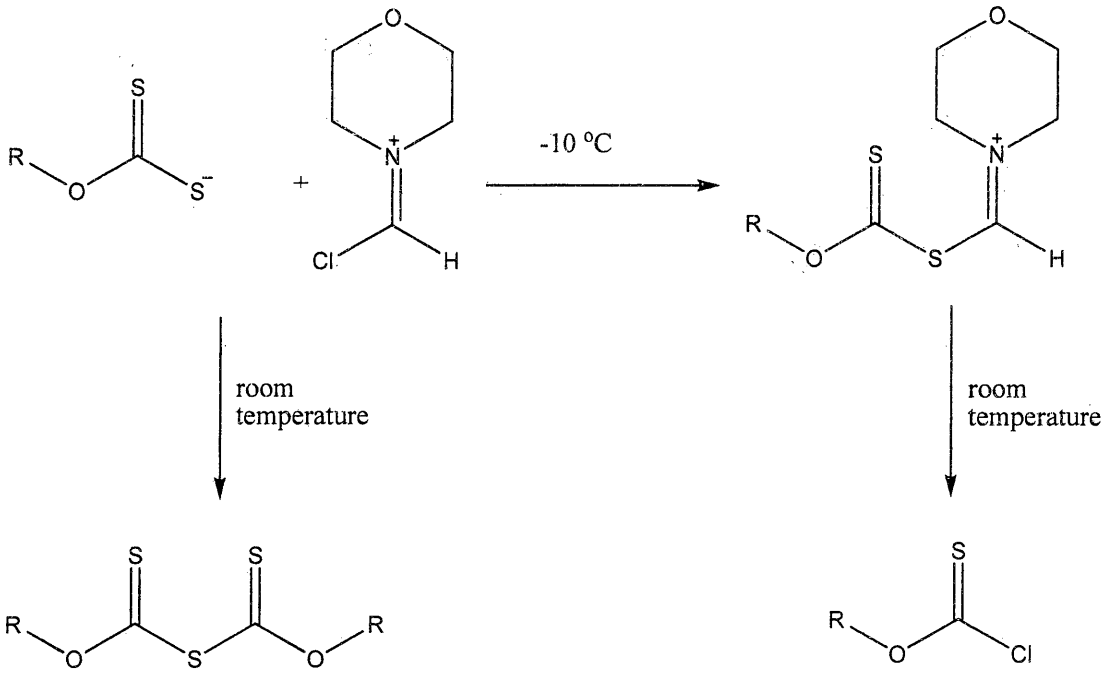
Figure 8: Decomposition of *bis*(methylthiothiocarbonyl)sulfane



The fact that the order of addition is a significant factor in the synthetic procedure also supports the idea that the competitive side reaction occurs. In the failed procedure, the Vilsmeier reagent is added directly to the trithiocarbonate salt meaning that any amount of methyl bromodithoformate formed is completely surrounded and consumed by methyl trithicarbonate salt. Conversely, the successful procedure has the trithiocarbonate salt added to the Vilsmeier reagent, which avoids the competitive reaction until the amount of methyl bromodithoformate begins to surpass that of the Vilsmeier Reagent. At that point the competition reaction, similar to the Jensen method, is unavoidable. Using an extreme excess of Vilsmeier reagent may prove to enhance the yield to some extent, however this does not solve the actual problem of the product reacting with the reagents.

There is, however, another potential advantage to the Vilsmeier reagent that does not exist in other synthetic methods. Previous studies in our lab have shown that the Vilsmeier-thiocarbonyl intermediate can be stabilized or 'frozen' at temperatures below -10 °C, avoiding decomposition into the reactive product.[9] The synthesis of methyl chlorothioformate is shown below.

Figure 9: Synthesis of Chlorothioformates from Xanthates[9]



The side product in this reaction is very similar to the proposed *bis*(methylthiothiocarbonyl)sulfane side product in our study. To confirm this hypothesis, further work is necessary. However, if successful this should eliminate the competition reaction entirely to produce better yields.

One final note to make is that methyl bromodithioformate does react with alcohols in a single step acylation to give xanthate protected alcohols. Though the yield for the reaction was only 17%, the reaction was attempted only once. Considerable work is still necessary in order to optimize the reaction conditions, but the initial results are very promising.

[1] Sasaki, Toru; Furukata, Kohsuke; Ishii, Shinichi; Iimori, Takamasa; Ikegami, Shiro; Nozaki, Tadashi; Senda, Michio. **Regioselective acetylation of 7-deacetylforskolin with 11C- acetyl chloride**. Journal of Labelled Compounds & Radiopharmaceuticals (1996), 38(4), 337-47.

[2] Ishihara, Kazuaki; Kurihara, Hideki; Yamamoto, Hisashi. **An extremely simple, convenient, and selective method for acetylating primary alcohols in the presence of secondary alcohols.** Journal of Organic Chemistry (1993), 58(15), 3791-3.

[3] Barany, George; Schroll, Alayne L.; Mott, Andrew W.; Halsrud, David A. **A general strategy for elaboration of the dithiocarbonyl functionality, -(C:O)SS-: application to the synthesis of bis(chlorocarbonyl)disulfane and related derivatives of thiocarbonic acids.** Journal of Organic Chemistry (1983), 48(24), 4750-61.

[4] Beckwith, Athelstan L. J.; Bowry, Vincent W.; Schiesser, Carl H. **Ring closure of the 6-methylenecyclodecyl radical.** Tetrahedron (1991), 47(1), 121-30.

[5] Kanie, Kiyoshi; Tanaka, Yoichiro; Suzuki, Kazundo; Kuroboshi, Manabu; Hiyama, Tamejiro. **A convenient synthesis of trifluoromethyl ethers by oxidative desulfurization-fluorination of dithiocarbonates.** Bulletin of the Chemical Society of Japan (2000), 73(2), 471-484.,

[6] Yamase, Yoshiaki. **Friedel-Crafts acylation. II. Relative reactivity for some acyl halides.** Bulletin of the Chemical Society of Japan (1961), 34 480-4.

[7] Jensen, K. A.. **Constitution of several addition compounds of tertiary amines and phosphines.** Journal fuer Praktische Chemie (Leipzig) (1937), 148 101-6.

[8] Sato, S.; Furukawa, N. **Thiocarbonic acids and derivatives.** Science of Synthesis (2005), 18 821-968.

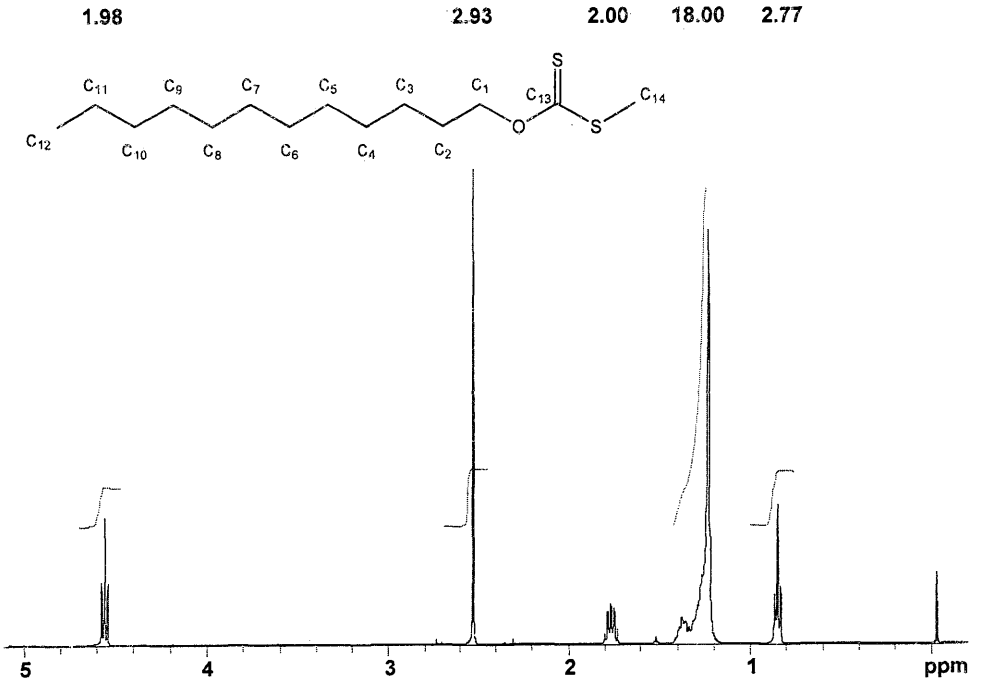
[9] Fikse, Megan A.; Bylund, William E.; Holubowitch, Nicolas E.; Abelt, Christopher J. **Synthesis of chlorothioformates from xanthates.** Synthesis (2006), (24), 4118-4120.

[10] Knoth, W.; Gattow, G.. **On chalcogenolates. 183. Bis(methylthiothiocarbonyl)sulfanes**. Zeitschrift fuer Anorganische und Allgemeine Chemie (1987), 554 172-5.

Appendix

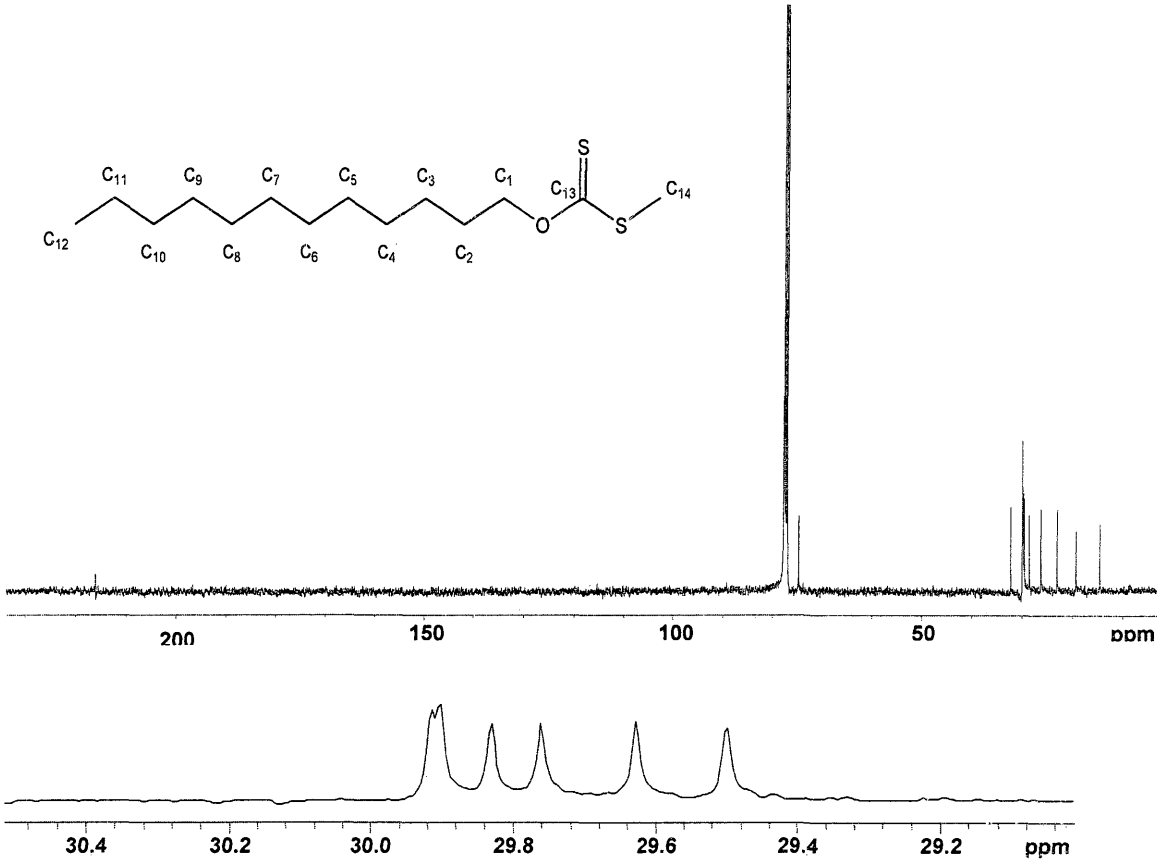
Supplemental ^{1}H-NMR, ^{13}C-NMR, and GC-MS Data

Figure A 1: ^{1}H-NMR of I



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_1	Triplet	1842.53	4.605	13.911
		1835.98	**4.588**	**27.283**
		1829.32	4.572	13.161
C_{14}	Singlet	**1023.88**	**2.559**	**109.619**
C_2	Pentet	732.99	1.832	1.750
		726.54	1.816	6.473
		719.59	**1.798**	**7.953**
		711.48	1.778	8.070
		704.96	1.762	3.204
C_3-C_{11}	Multiplet	**505.07**	**1.262**	**86.348**
C_{12}	Triplet	359.38	0.898	9.724
		352.84	**0.882**	**31.327**
		345.77	0.864	13.31

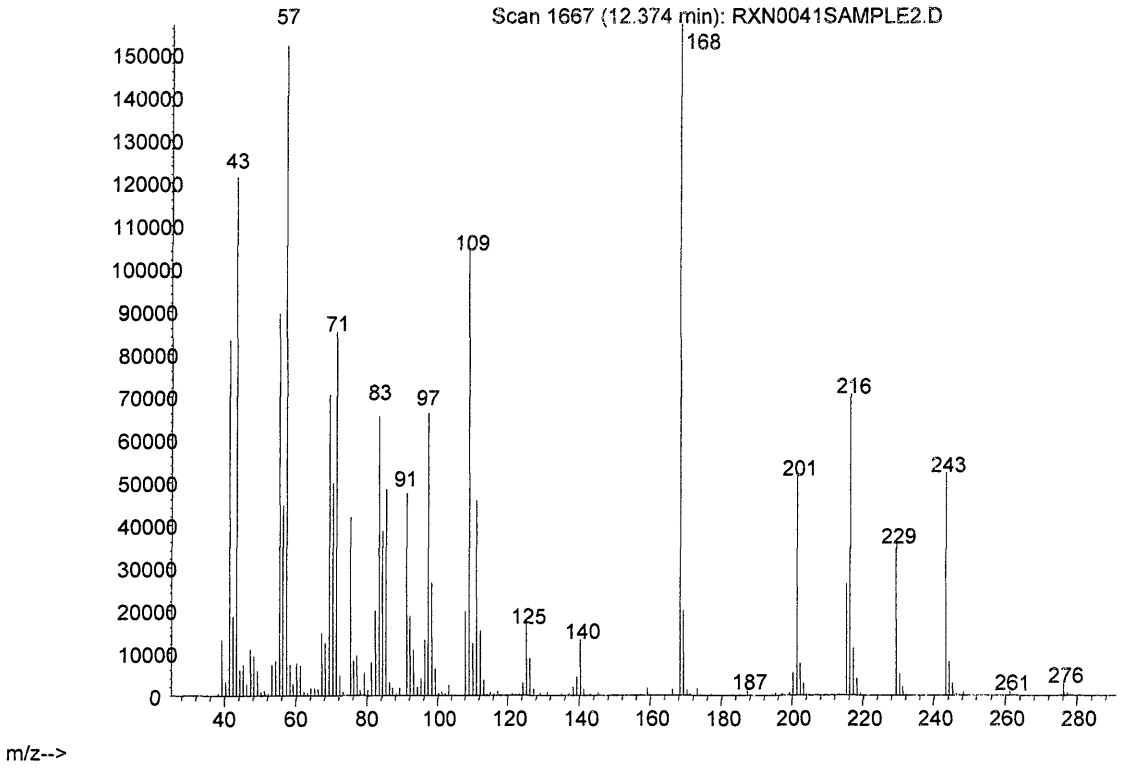
Figure A 2: ^{13}C-NMR of I



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_{12}	1452.58	14.436	4.036
2	C_{14}	1930.73	19.188	3.502
3	C_{11}	2312.83	22.985	5.196
4	$C_{2\text{-}9}$	2632.36	26.161	4.877
5	$C_{2\text{-}9}$	2869.49	28.517	5.048
6	$C_{2\text{-}9}$	2968.46	29.501	6.569
7	$C_{2\text{-}9}$	2981.32	29.629	6.743
8	$C_{2\text{-}9}$	2993.92	29.754	6.474
9	$C_{2\text{-}9}$	3001.65	29.831	6.250
10[a]	$C_{2\text{-}9}$	3008.45	29.898	8.108
11	C_{10}	3239.15	32.191	5.484
12	C_1	7500.36	74.539	4.965
13	C_{13}	21734.32	215.998	1.623

[a] Doublet when resolved

Figure A 3: Mass Spectrum of I



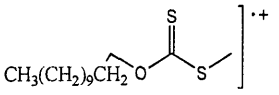
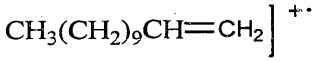
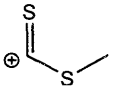
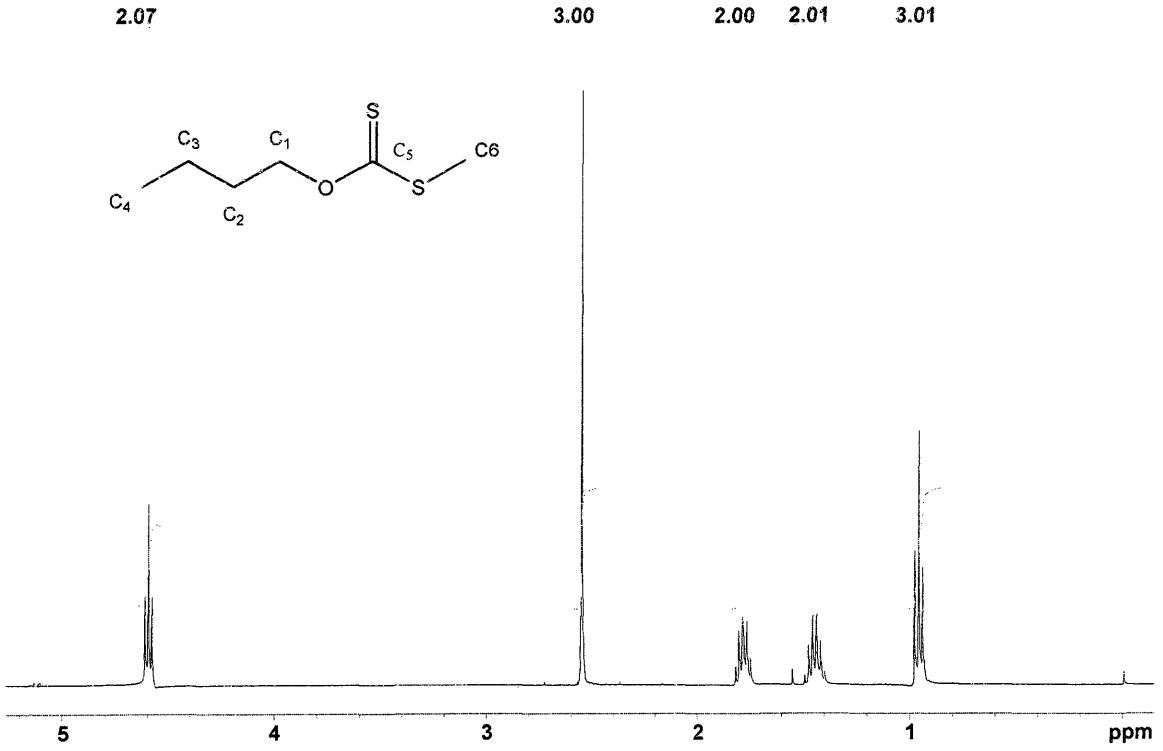
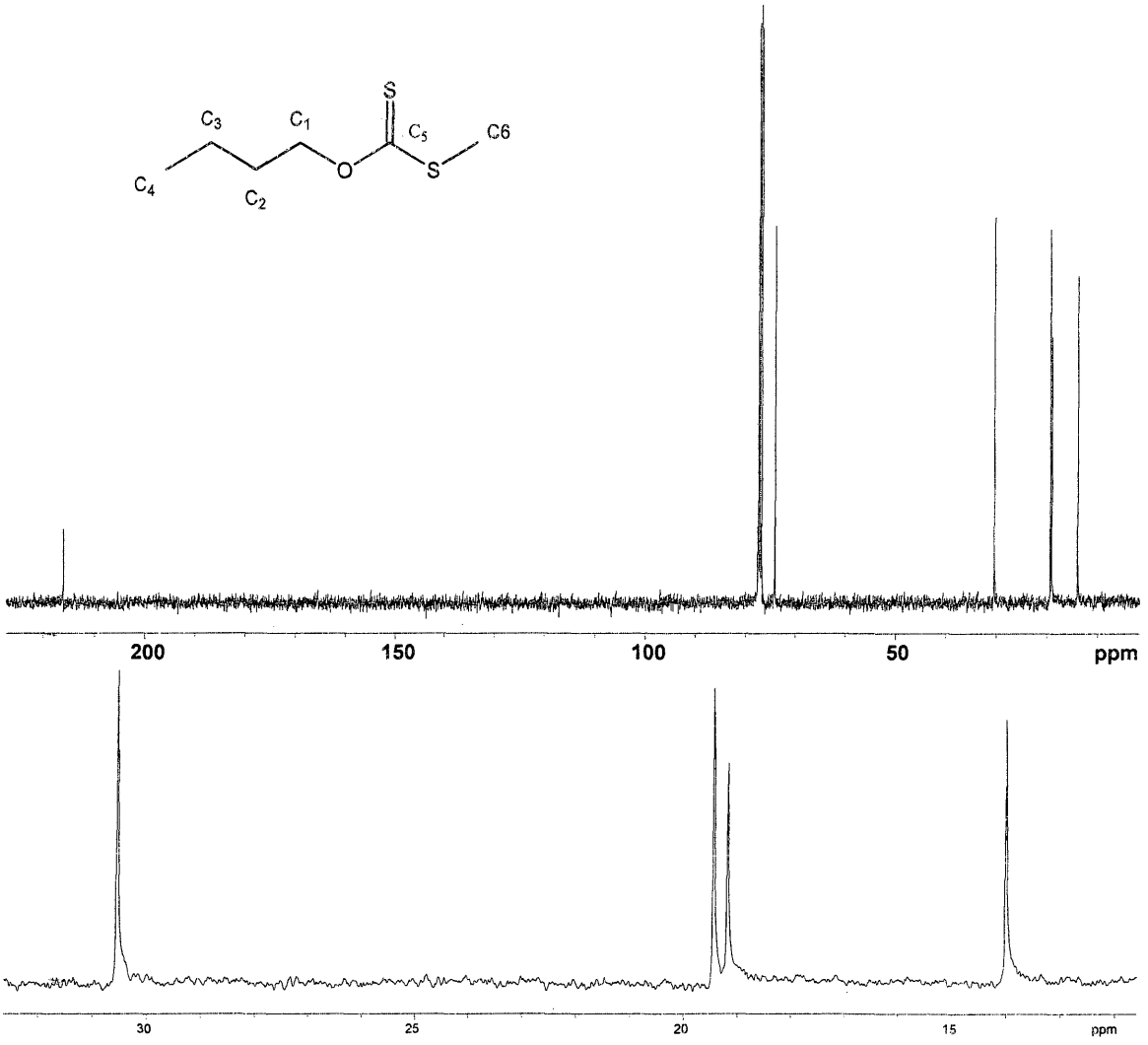
Mass	Ion / Radical	
276		Molecular Ion
168		
91		

Figure A 4: ^{1}H-NMR of II



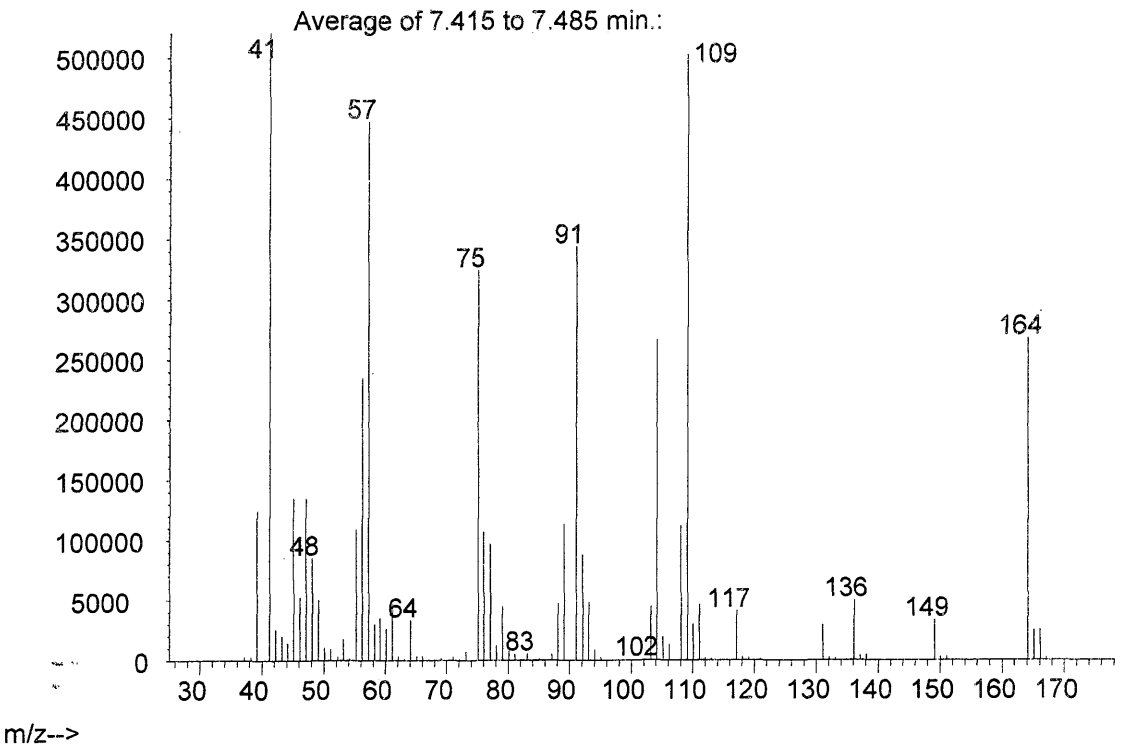
Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_4	Triplet	375.58	0.939	19.694
		382.63	**0.956**	**43.065**
		390.14	0.975	23.640
C_3	Sextet	558.82	1.397	2.196
		566.02	1.415	7.620
		573.37	**1.433**	**12.182**
		580.97	**1.452**	**11.915**
		588.29	1.470	6.914
		595.60	1.489	1.625
C_2	Pentet	698.13	1.745	4.640
		704.85	1.762	11.027
		712.60	**1.781**	**11.764**
		719.51	1.798	9.226
		726.63	1.816	3.244
C_6	Singlet	**1020.23**	**2.550**	**105.708**
C_1	Triplet	1831.47	4.577	15.631
		1838.23	**4.594**	**30.599**
		1844.77	4.610	16.334

Figure A 5: ^{13}C-NMR of II



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_4	1409.26	14.005	53.549
2	C_6	1929.09	19.172	44.658
3	C_3	1956.00	19.439	63.630
4	C_2	3073.42	30.544	63.943
5	C_1	7465.07	74.189	61.911
6	C_5	21732.81	215.983	12.379

Figure A 6: Mass Spectrum of II



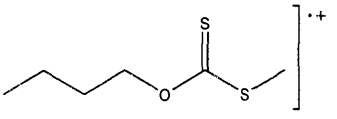
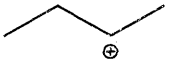
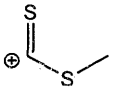
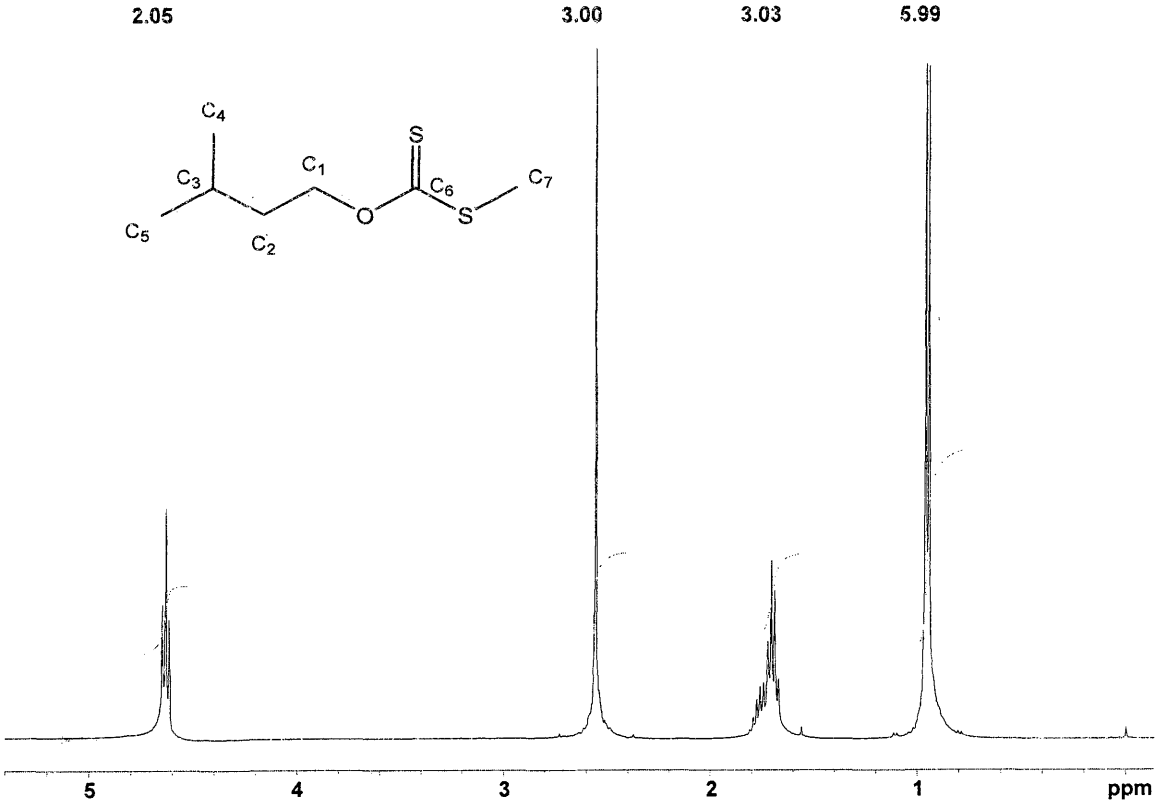
Mass	Ion / Radical	
164		Molecular Ion
57		
91		

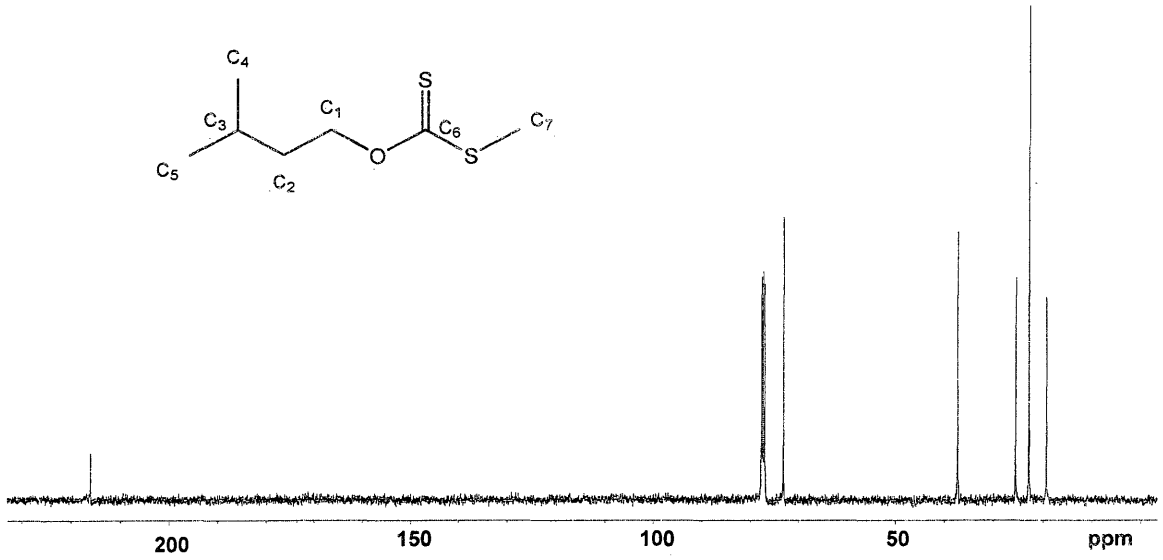
Figure A 7: ^{1}H-NMR of III



Parent Carbon	Splitting	HZ	PPM	Relative Intensity
C_4,C_5	Doublet	**378.17**	**0.945**	**97.847**
		384.45	**0.961**	**98.341**
C_2,C_3	Mutiplet	669.02	1.672	8.753
	Overlap	675.50	1.688	21.430
		682.16	**1.705**[a]	**25.992**
		689.04	1.722	14.195
		697.78	1.744	8.048
		704.58	1.761	7.579
		711.39	1.778	5.678
		718.01	1.794	3.095
C_7	Singlet	**1022.59**	**2.556**	**102.946**
C_1	Triplet	1847.06	4.616	17.507
		1853.57	**4.632**	**33.908**
		1860.12	4.649	19.679

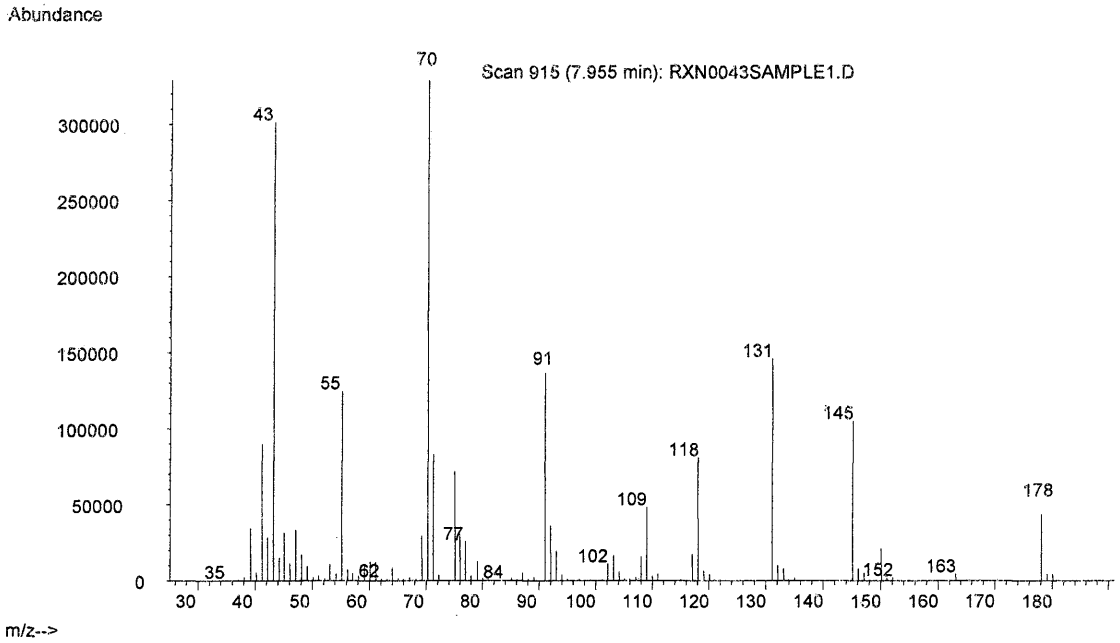
[a] Central peak for Protons of C_2

Figure A 8: ^{13}C-NMR of III



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_7	1937.89	19.259	39.974
2	C_4,C_5	2295.29	22.811	100.691
3	C_3	2562.49	25.466	43.564
4	C_2	3742.31	37.192	52.403
5	C_1	7355.38	73.099	53.999
6	C_6	21747.04	216.124	0.933

Figure A 9: Mass Spectrum of III



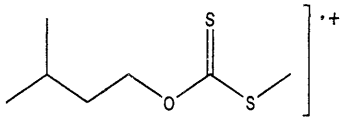
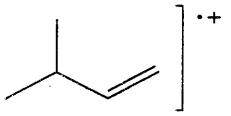
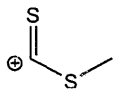
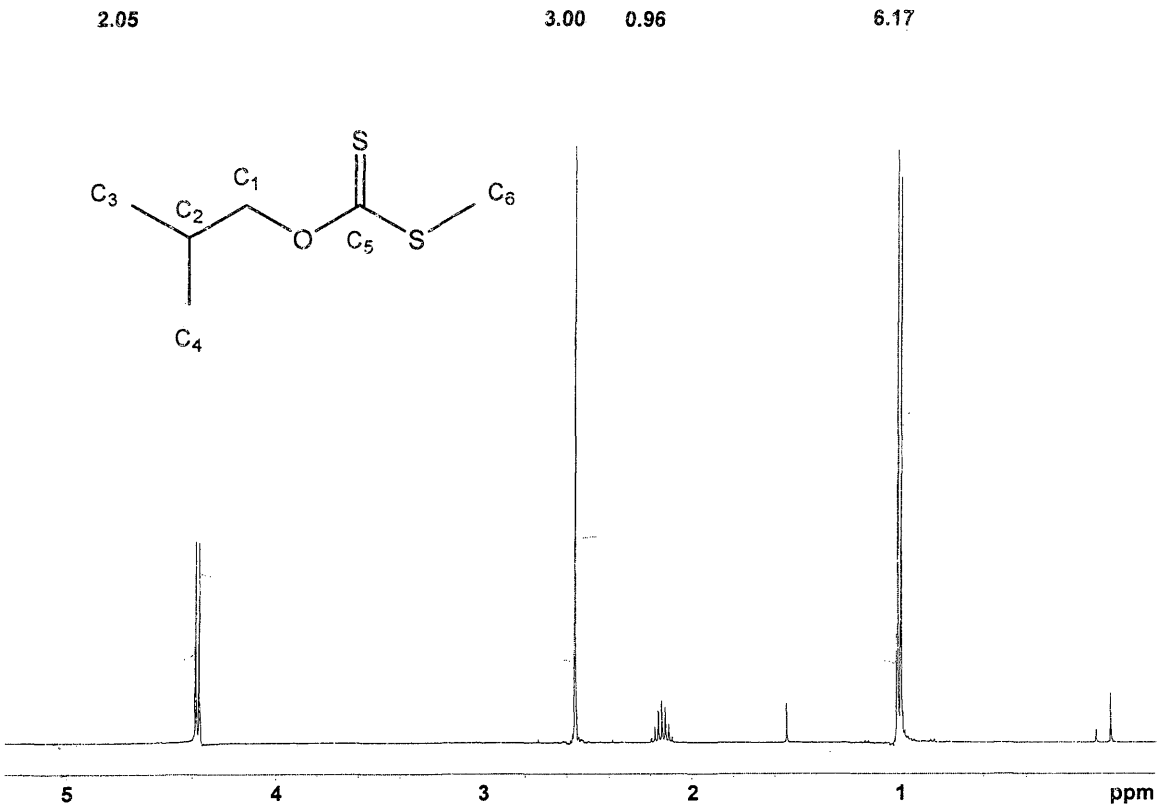
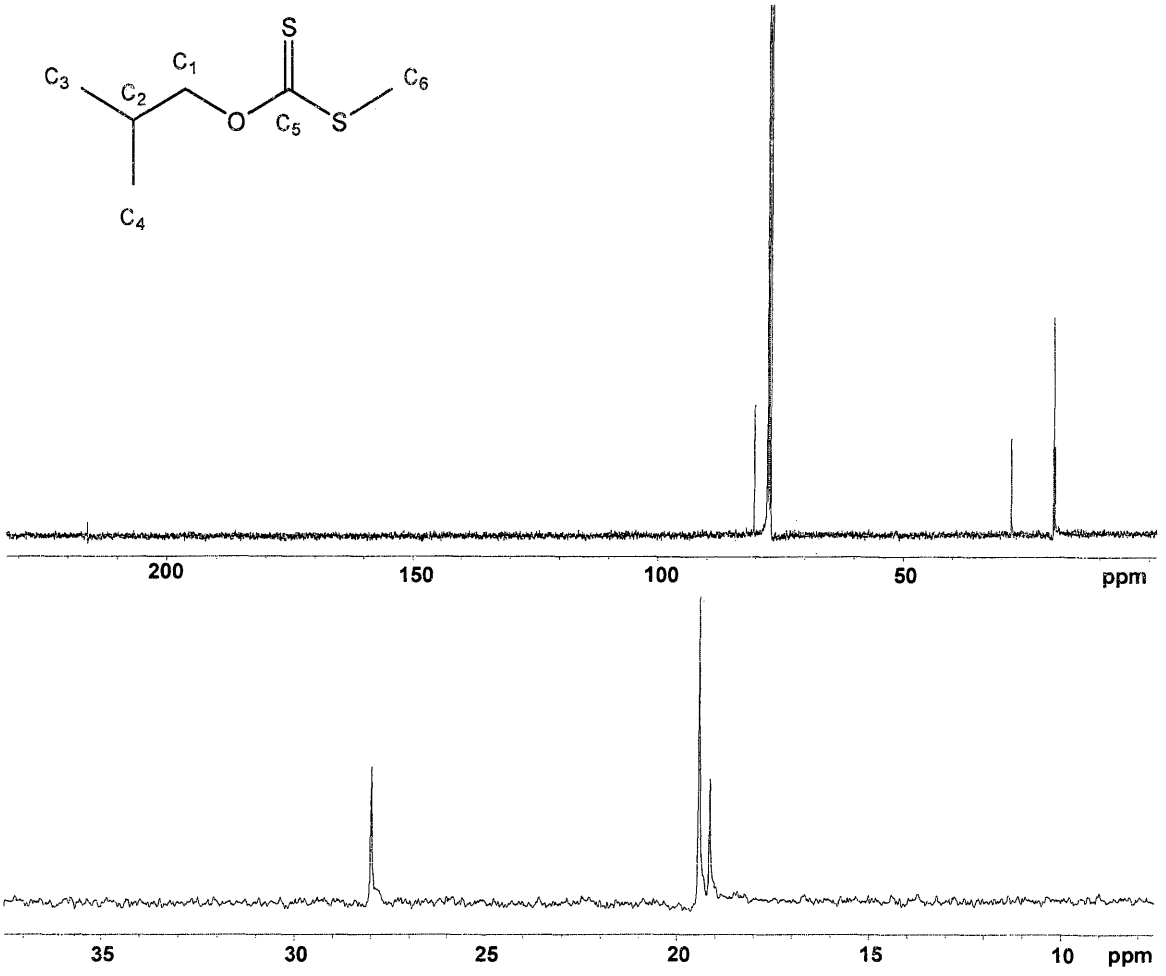
Mass	Ion / Radical	
178		Molecular Ion
70		
91		

Figure A 10: ^{1}H-NMR of IV



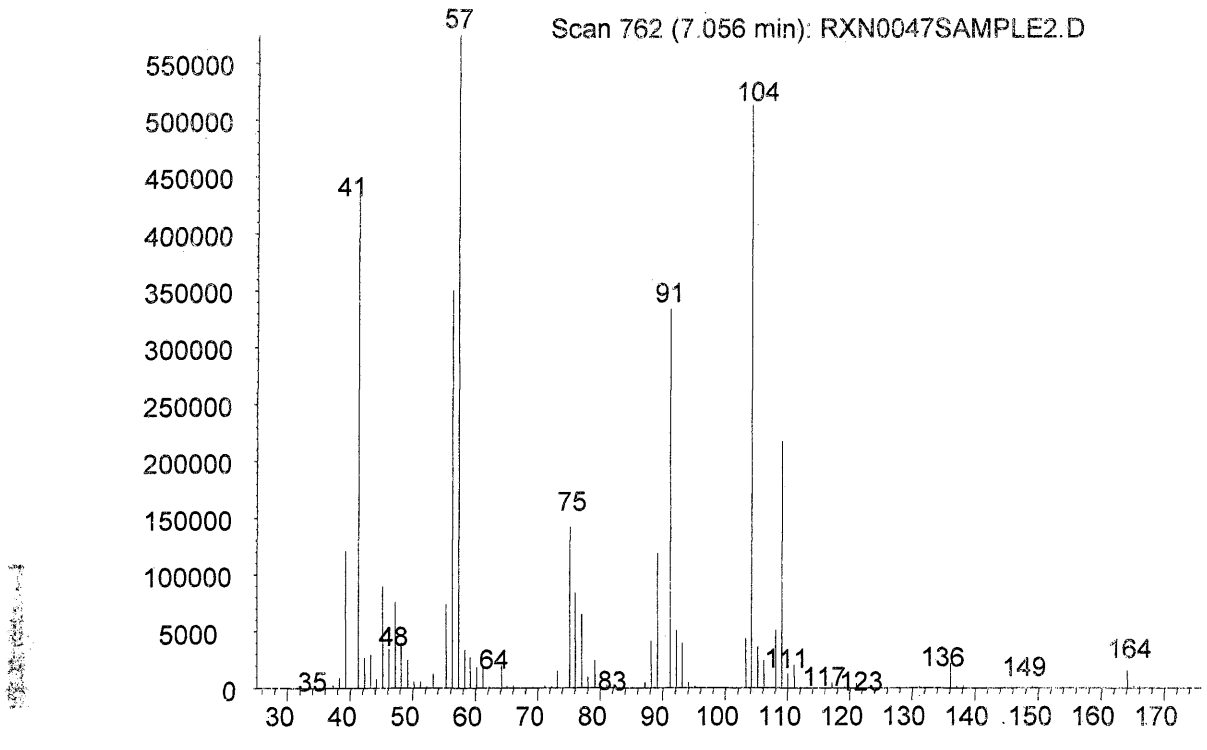
Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_3,C_4	Doublet	**398.51**	**0.996**	**103.274**
		405.35	**1.013**	**104.728**
C_2	Nonet	830.10	2.075	0.125
		839.01	2.097	1.020
		845.82	2.114	3.079
		852.30	2.130	6.322
		858.82	**2.146**	**7.445**
		865.76	2.164	5.277
		872.51	2.181	2.842
		879.29	2.198	0.792
		883.84	2.209	0.115
C_6	Singlet	**1025.67**	**2.563**	**108.074**
C_1	Doublet	**1747.68**	**4.368**	**34.599**
		1754.37	**4.385**	**33.577**

Figure A 11: ^{13}C-NMR of IV



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_6	1928.45	19.165	15.322
2	C_3,C_4	1956.93	19.448	38.423
3	C_2	2818.81	28.014	16.472
4	C_1	8079.90	80.299	22.203
5	C_5	21737.37	216.028	2.141

Figure A 12: Mass Spectrum of IV



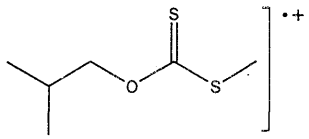
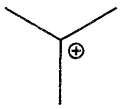
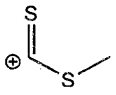
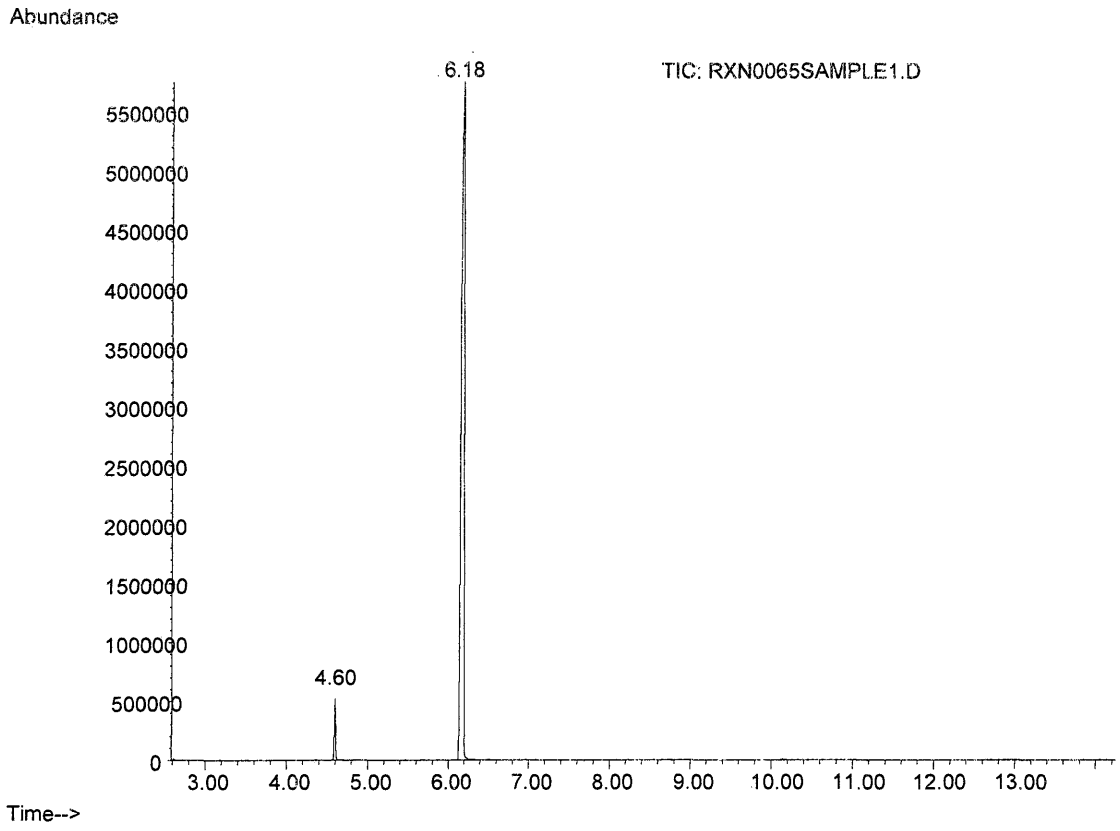
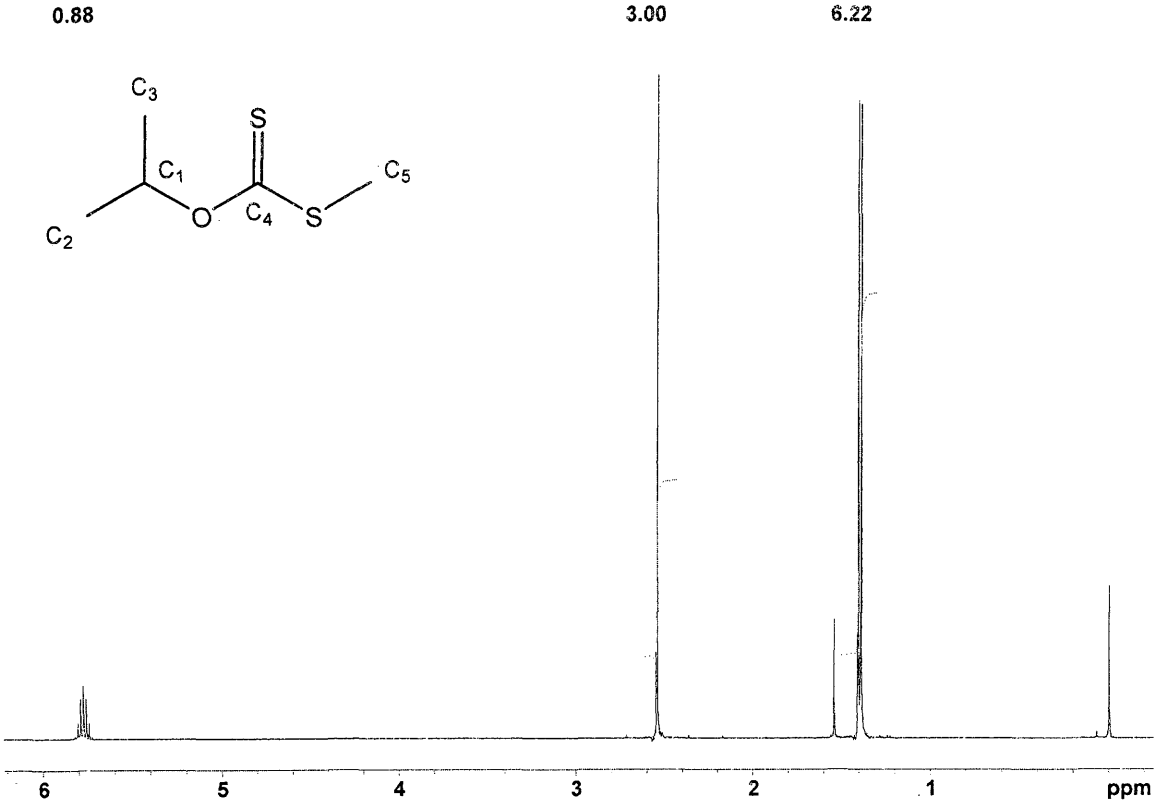
Mass	Ion / Radical	
164		Molecular Ion
57		
91		

Figure A 13: Gas Chromatograph of V



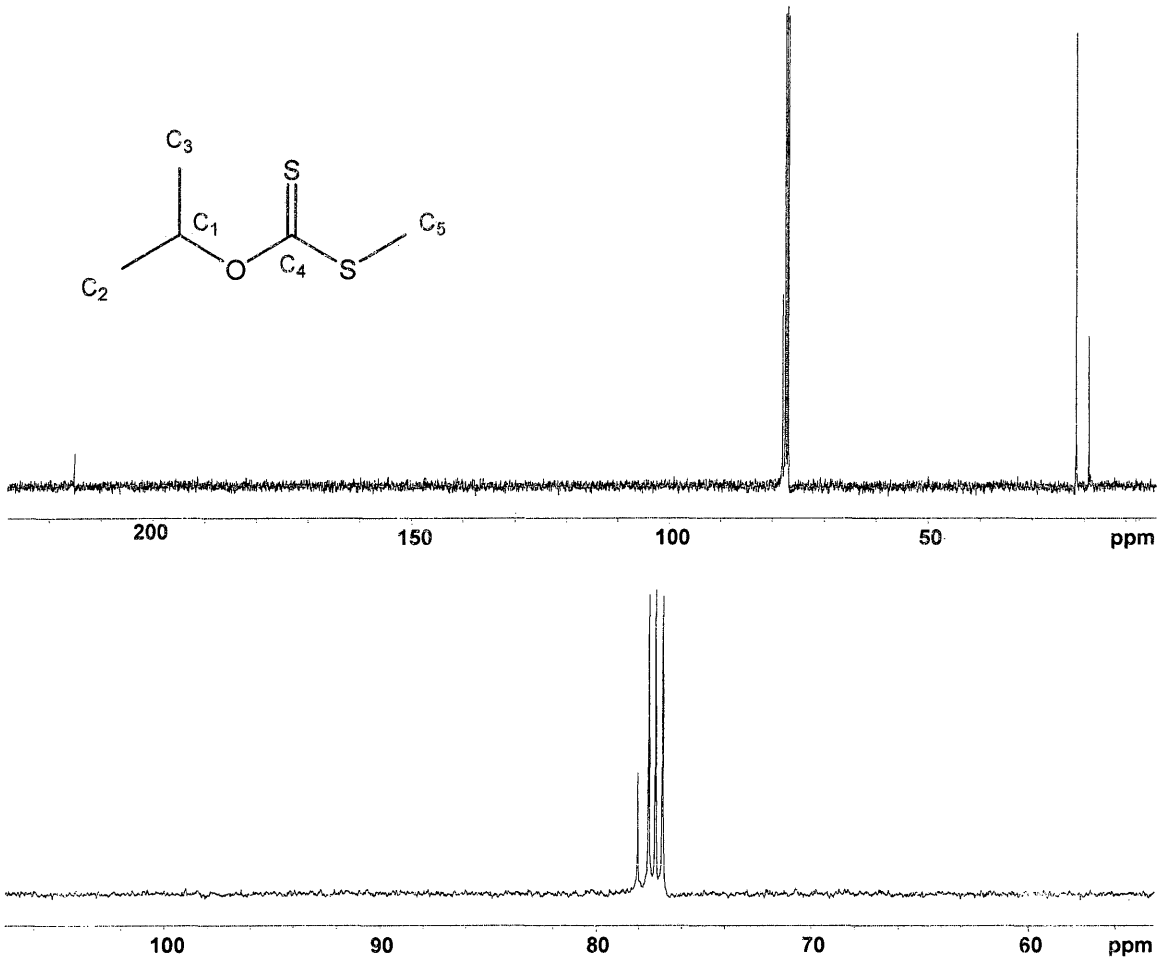
Retention time (min)	**Name**
4.60	O-(1-methyl-ethyl)-s-methyl-thiocarbonate
6.18	V

Figure A 14: ^{1}H-NMR of V



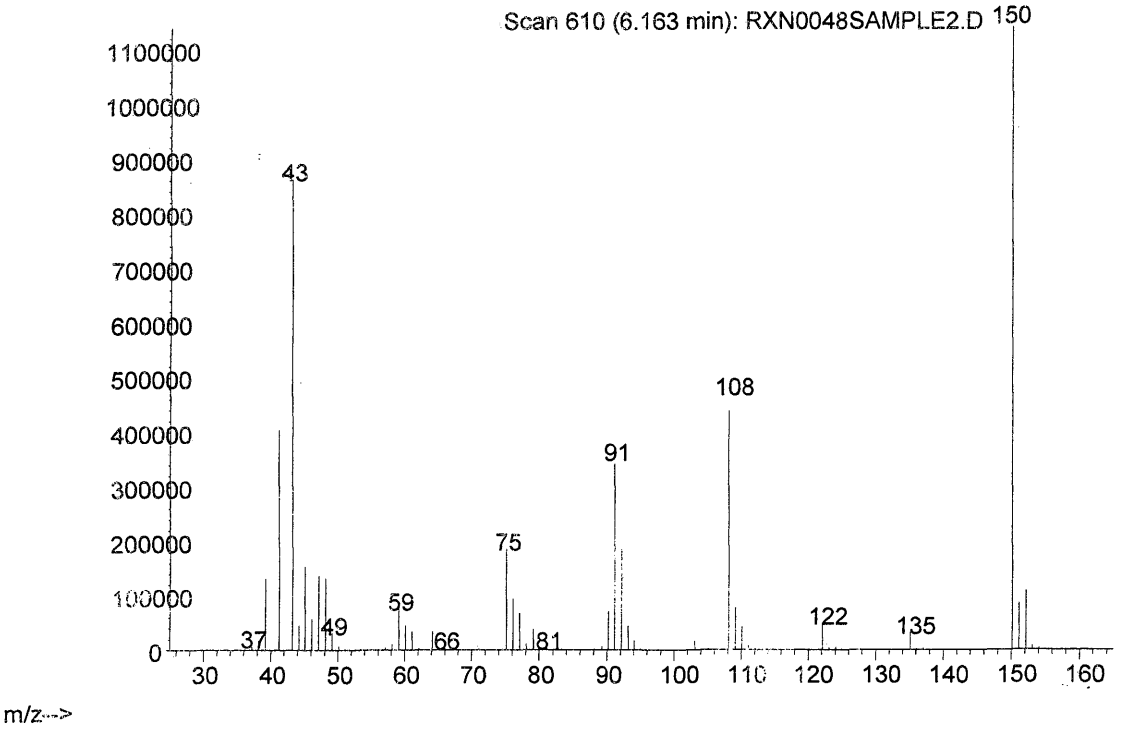
Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_2,C_3	Doublet	**555.54**	**1.388**	**102.743**
		561.83	**1.404**	**103.604**
C_5	Singlet	**1018.28**	**2.545**	**106.920**
C_1	Septet	2293.26	5.731	0.267
		2299.57	5.747	2.448
		2305.87	5.763	6.347
		2312.15	**5.779**	**8.439**
		2318.44	5.794	6.298
		2324.73	5.810	2.573
		2330.88	5.825	0.588

Figure A 15: ^{13}C-NMR of V



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_5	1919.05	19.072	31.371
2	C_2,C_3	2172.77	21.593	98.431
3	C_1	7854.75	78.061	41.231
4	C_4	21655.63	215.216	6.967

Figure A 16: Mass Spectrum of V



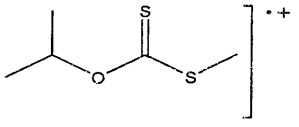
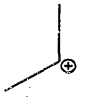
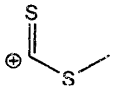
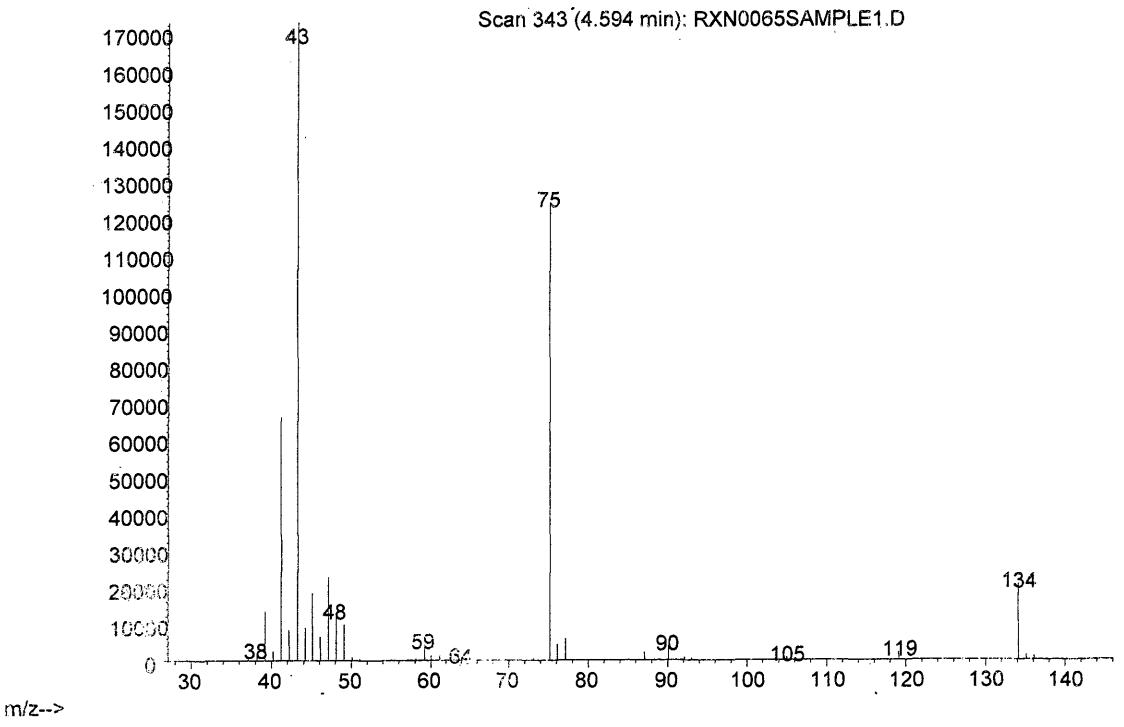
Mass	Ion / Radical	
150		Molecular Ion
43		
91		

Figure A 17: Mass Spectrum of O-(1-methyl-ethyl)-s-methyl-thiocarbonate



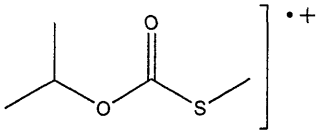
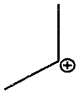
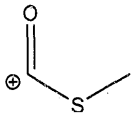
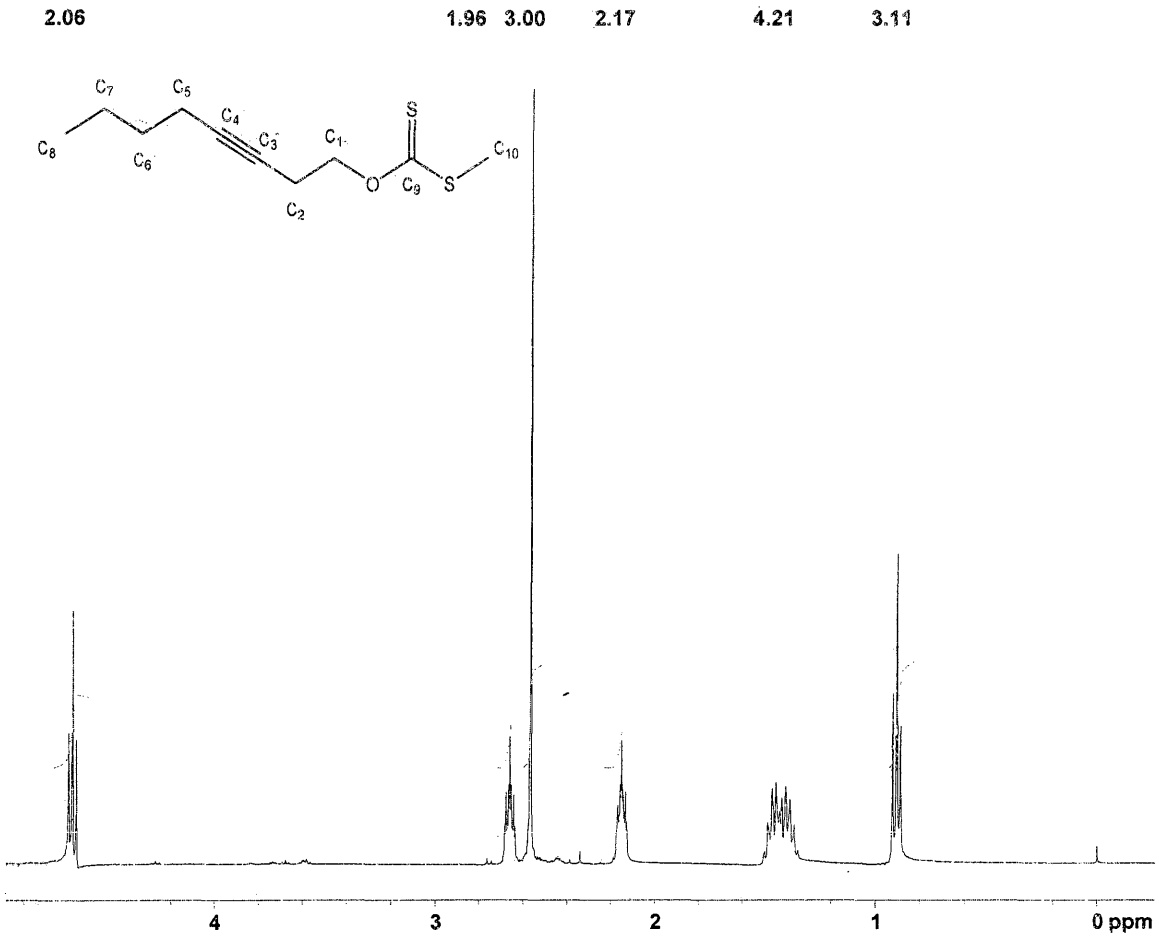
Mass	Ion / Radical	
134		Molecular Ion
43		
75		

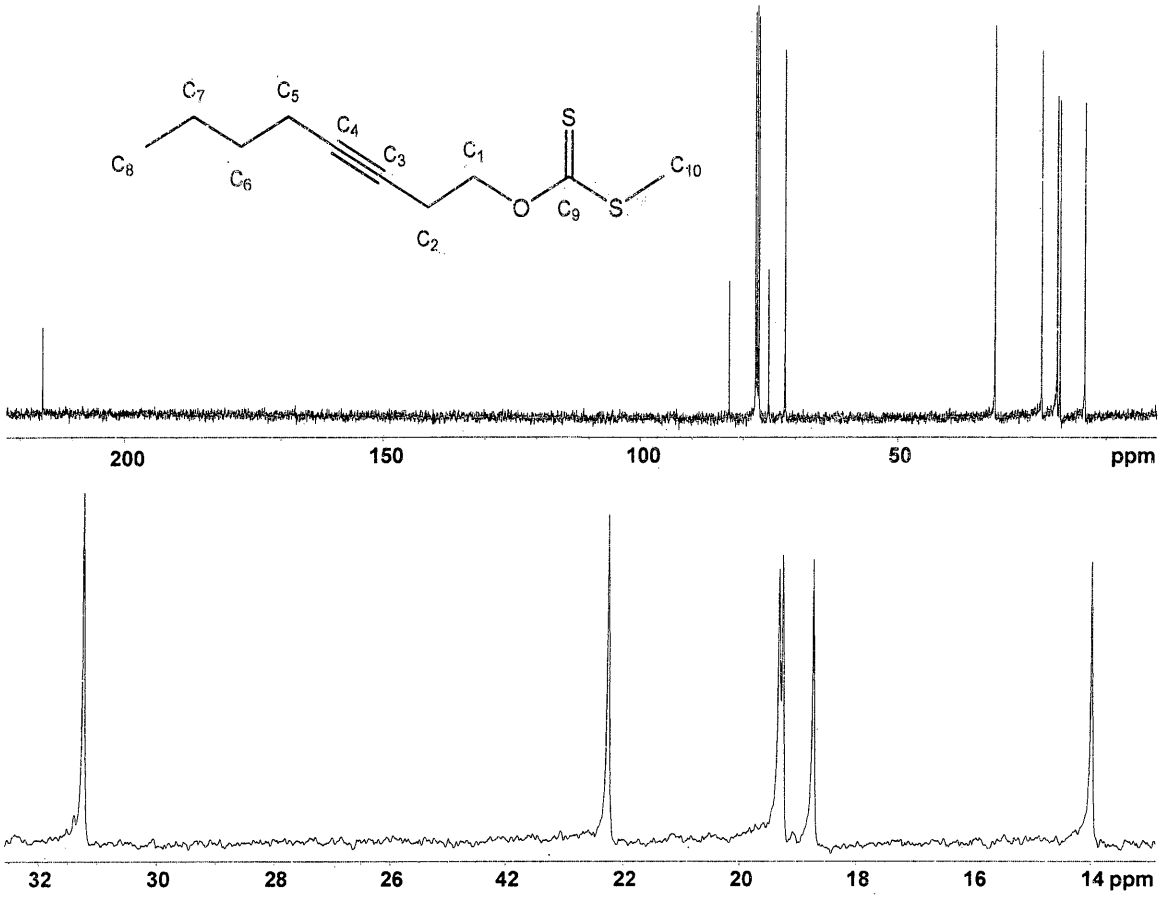
Figure A 18: ^{1}H-NMR of VI



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_8	Triplet	355.32	0.888	18.243
		362.24	**0.905**	**41.320**
		369.66	0.924	22.752
C_6,C_7	Multiplet	540.05	1.350	1.694
		546.76	1.366	5.089
		554.58	1.386	8.328
		561.85	**1.404**	**9.946**
		569.13	1.422	8.448
		572.86	1.432	6.752
		579.88	**1.449**	**10.670**
		586.46	1.466	9.677
		594.72	1.486	5.320
		600.26	1.500	1.613
C_5	Triplet of Triplets[a]	852.07	2.129	5.333
		854.29	**2.135**	**9.602**
		856.77	2.141	6.782
		858.73	2.146	9.987
		861.20	**2.152**	**16.101**
		863.50	2.158	10.181
		865.50	2.163	6.240
		867.57	**2.171**	**8.652**
		870.22	2.175	4.304
C_{10}	Singlet	**1027.24**	**2.567**	**100.462**
C_2	Triplet of Triplets[a]	1055.26	2.637	4.918
		1057.65	**2.643**	**9.022**
		1059.93	2.649	5.990
		1061.87	2.657	9.742
		1064.69	**2.661**	**18.008**
		1067.06	2.667	10.303
		1069.26	2.672	6.508
		1071.73	**2.678**	**9.369**
		1074.11	2.684	5.072
C_1	Triplet	1852.08	4.629	16.388
		1859.10	**4.646**	**33.501**
		1866.10	4.664	17.474

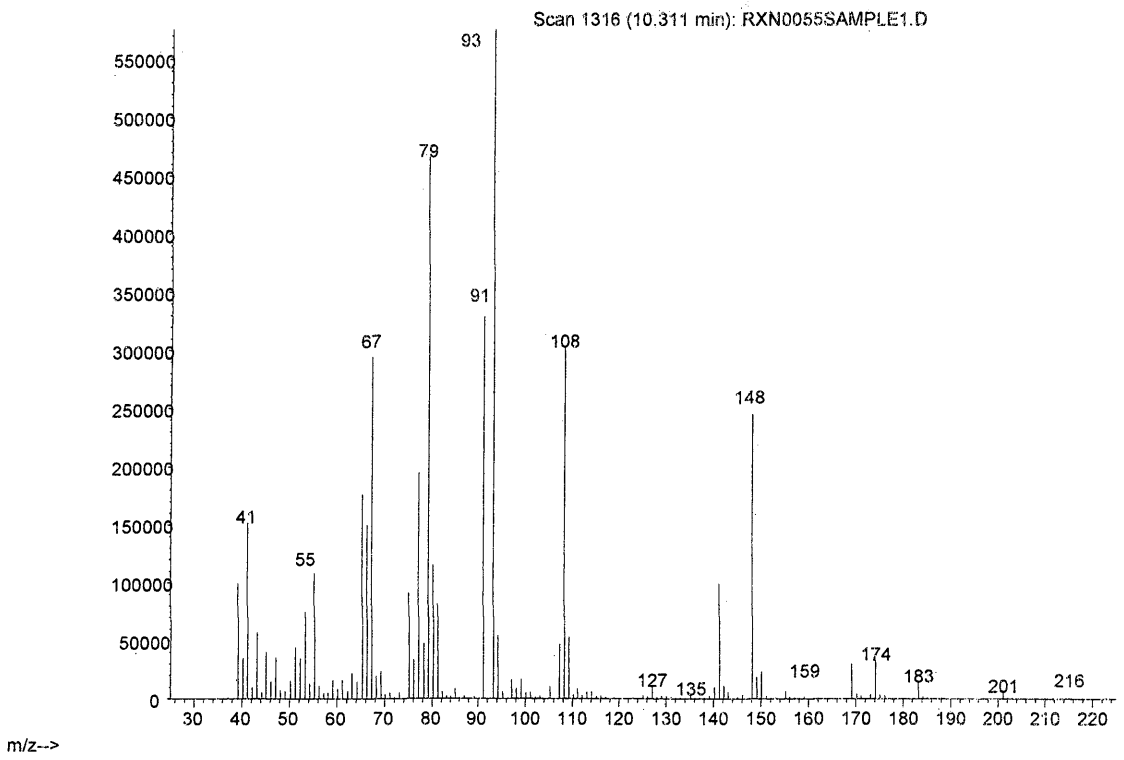
[a] Triplet of triplets due to long range coupling over triple bond

Figure A 19: ^{13}C-NMR of VI



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1405.58	13.969	75.300
2	C_{10}	1884.35	18.727	76.254
3	C_5	1937.18	19.252	78.370
4	C_2	1943.43	19.314	73.370
5	C_7	2238.15	22.243	89.329
6	C_6	3142.97	31.235	95.903
7	C_1	7233.48	71.887	88.269
8	C_4	7551.31	75.046	35.457
9	C_3	8327.02	82.755	32.545
10	C_9	21701.60	215.673	20.652

Figure A 20: Mass Spectrum of VI



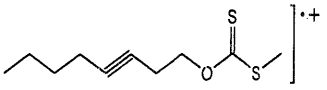
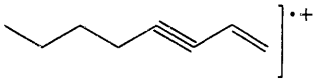
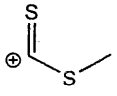
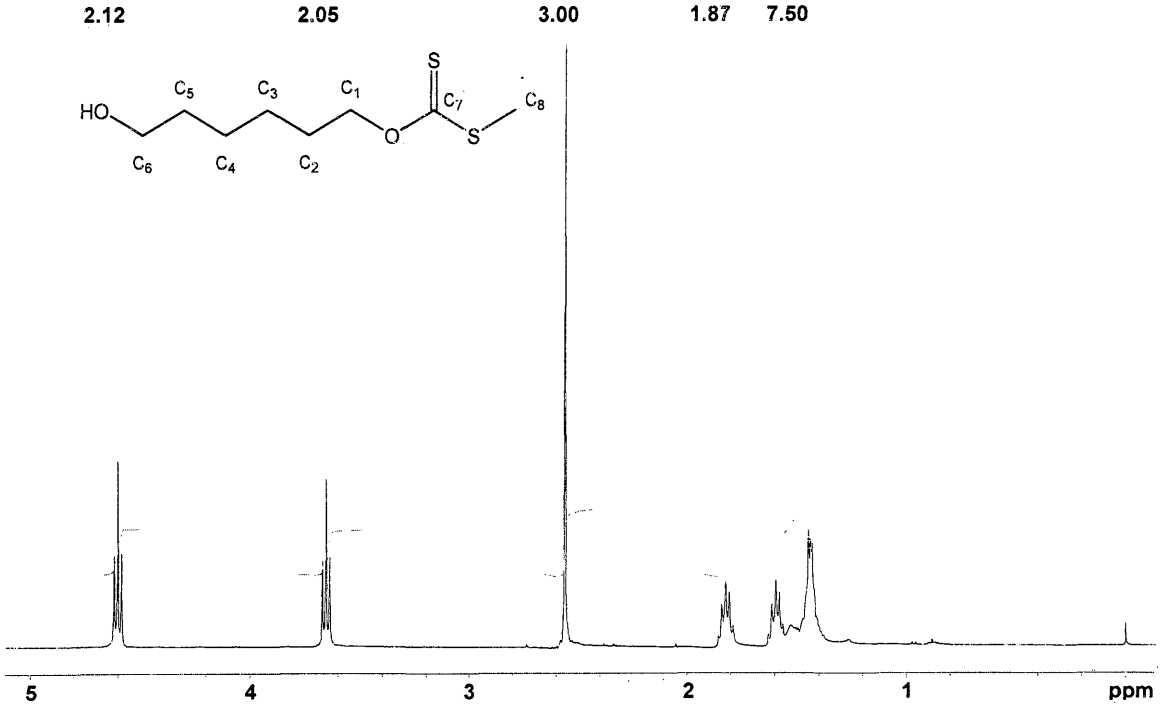
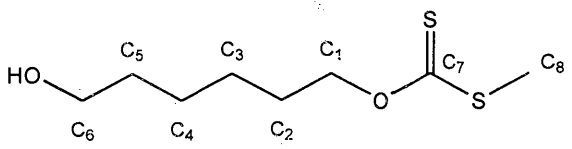
Mass	Ion / Radical	
216		Molecular Ion
108		
91		

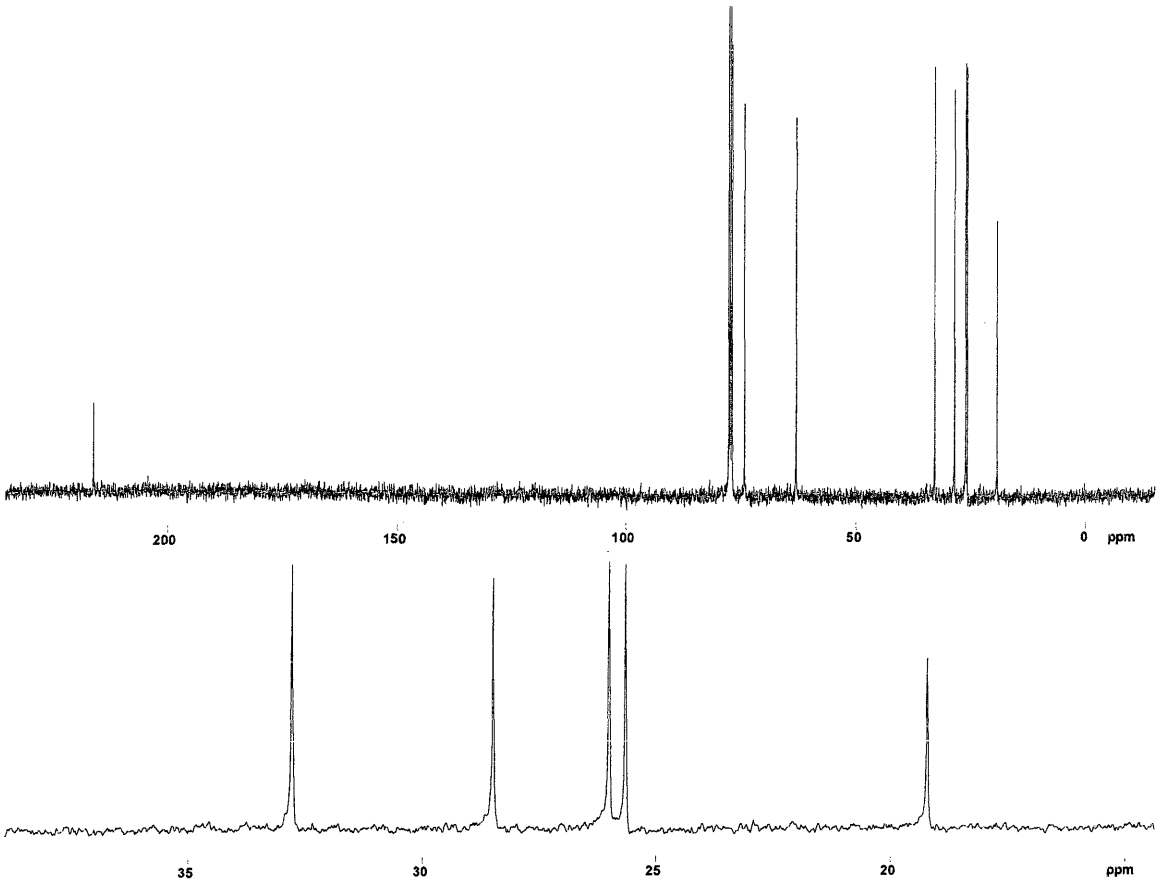
Figure A 21: ^{1}H-NMR of VII



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_3,C_4,	Multiplet	572.45	1.431	17.411
Hydroxy		575.98	1.439	17.960
Proton		579.82	1.449	19.009
C_5	Pentet	625.40	1.563	3.628
		631.99	1.579	9.009
		638.79	**1.596**	**10.865**
		645.59	1.613	6.859
		652.51	1.631	1.833
C_2	Pentet	716.02	1.789	3.482
		722.60	1.806	9.133
		729.91	**1.824**	**10.584**
		736.55	1.841	6.833
		743.59	1.858	1.618
C_8	Singlet	**1024.81**	**2.561**	**104.750**
C_6	Triplet	1456.56	3.640	15.455
		1463.06	**3.656**	**30.439**
		1469.36	3.672	15.318
C_1	Triplet	1834.57	4.585	14.946
		1841.16	**4.601**	**32.137**
		1847.72	4.618	16.966

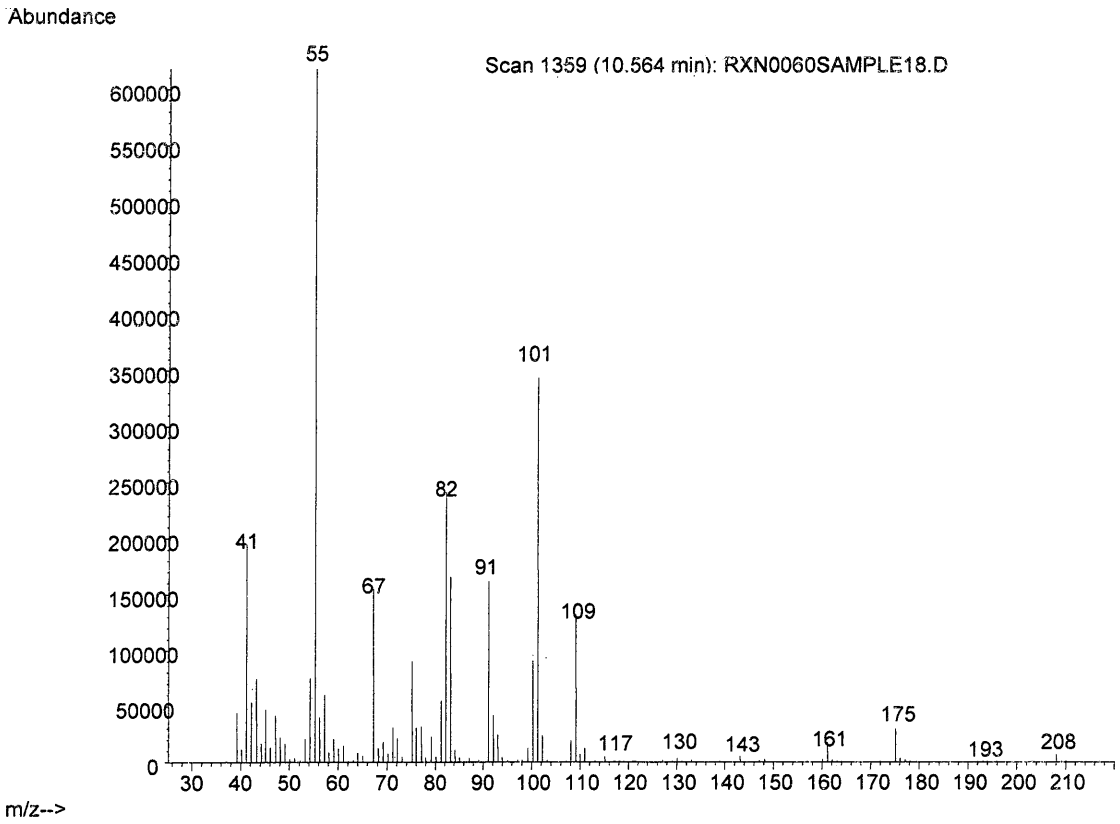
Figure A 22: ^{13}C-NMR of VII





Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1940.60	19.286	35.962
2	C_4	2588.73	25.727	58.630
3	C_3	2623.83	26.076	57.148
4	C_2	2872.68	28.549	55.362
5	C_5	3307.84	32.874	57.340
6	C_6	6346.20	63.069	51.003
7	C_1	7479.13	74.328	52.369
8	C_7	21741.18	216.066	12.573

Figure A 23: Mass Spectrum of VII



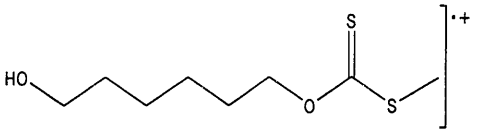
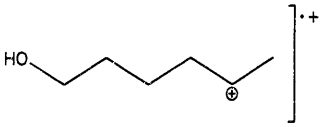
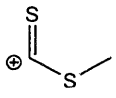
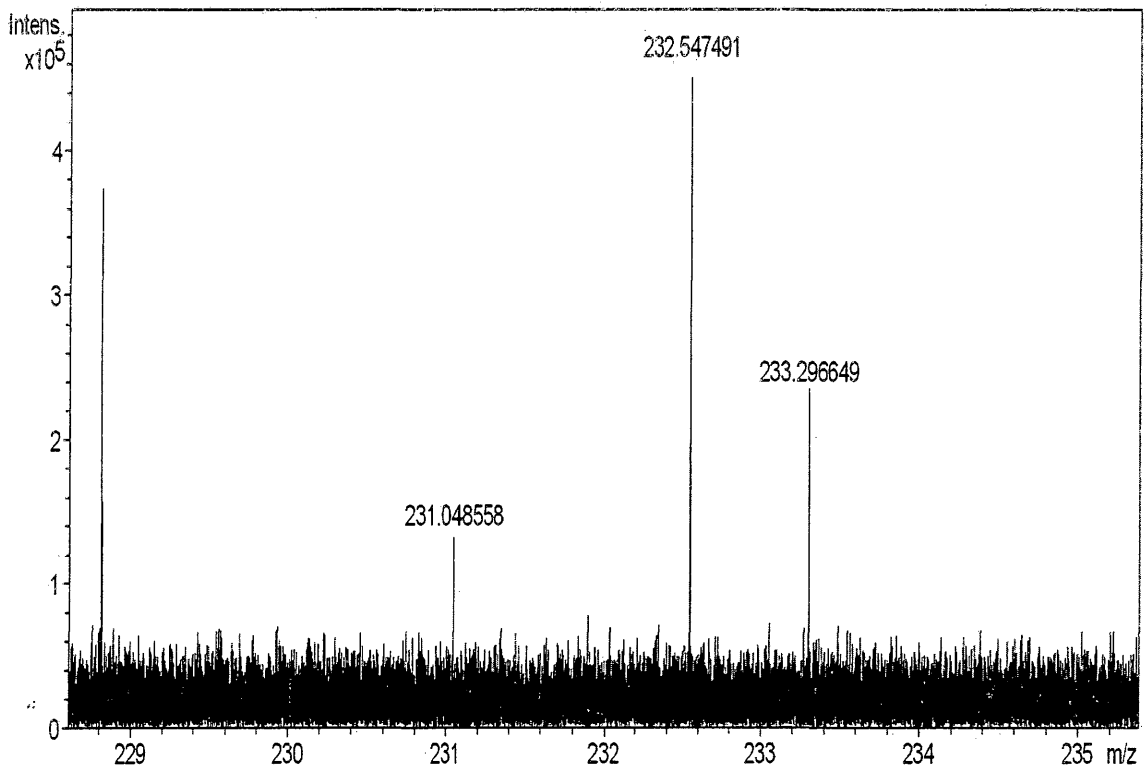
Mass	Ion / Radical	
208		Molecular Ion
101		
91		

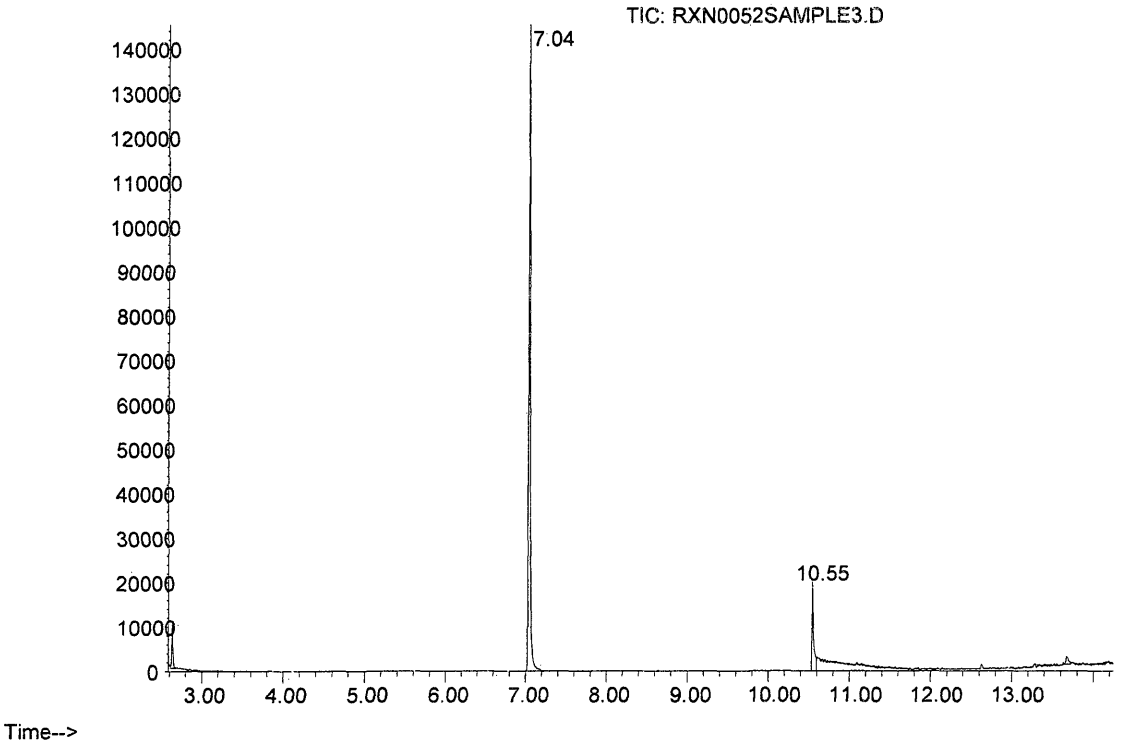
Figure A 24: Mass Spectrum of C8H16O2S2Na+



Exact mass of C8H16O2S2Na+ = 231.048392u
Observed mass: 231.048558u
Difference: <-1.0ppm

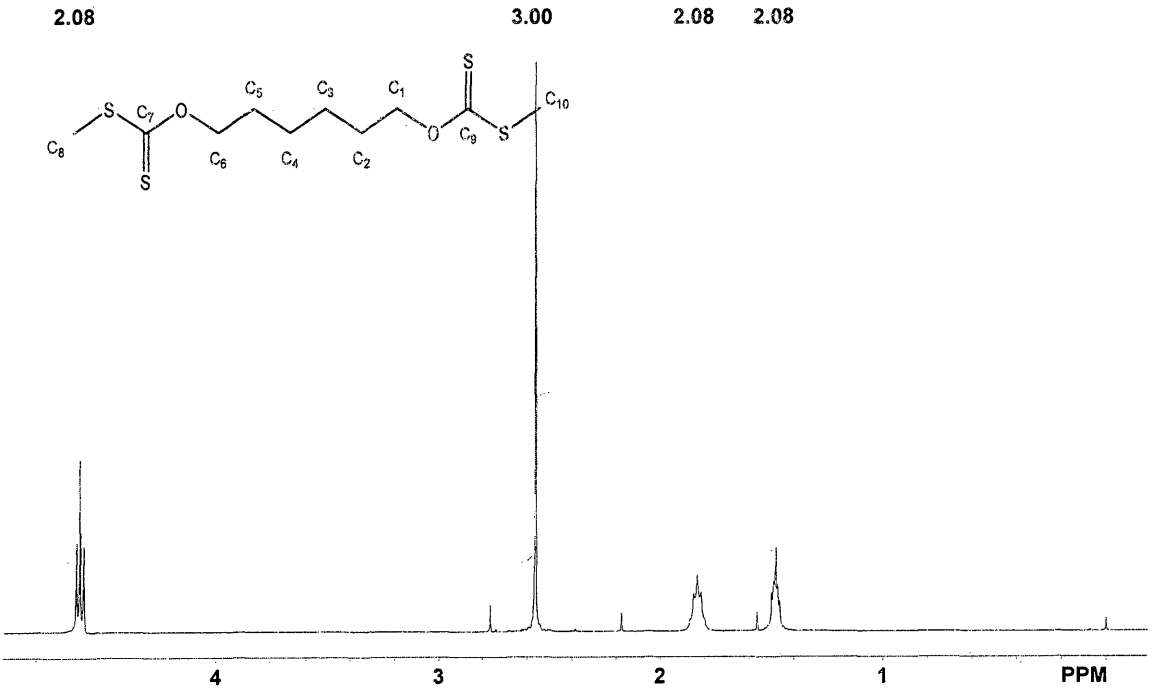
1:1 THF:MeOH with NaCl and analyzed by positive ion electrospray on a Bruker 12 Tesla APEX -Qe FTICR-MS with an Apollo II ion source

Figure A 25: Gas Chromatograph of Failed Synthesis of VII



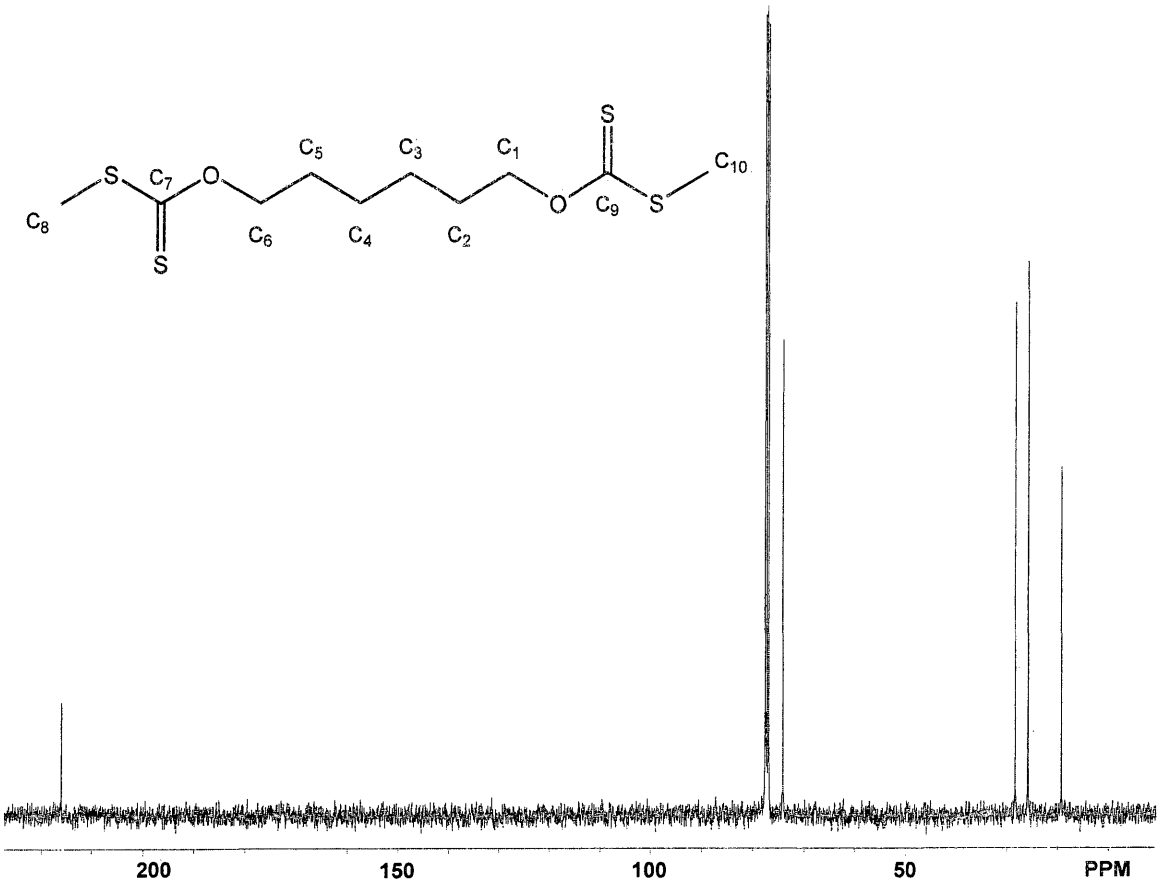
Retention time (min)	**Name**
7.04	Dimethyl trithiocarbonate
10.55	VII

Figure A 26: ^{1}H-NMR of VIII



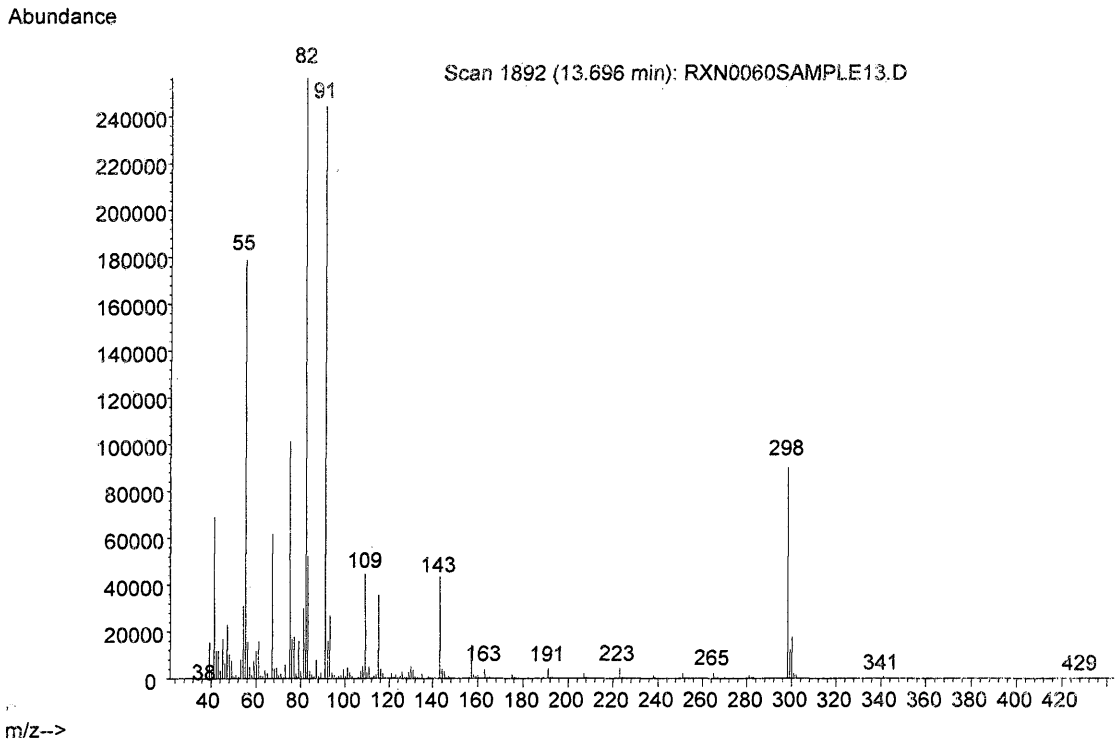
Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_3,C_4	Pentet	585.27	1.463	5.489
		589.11	1.472	8.273
		592.50	**1.481**	**15.108**
		596.09	1.490	8.848
		599.89	1.499	6.936
C_2,C_5	Pentet	719.70	1.799	2.260
		726.35	1.815	6.944
		733.50	**1.833**	**9.865**
		740.12	1.850	6.610
		747.23	1.868	2.148
C_8,C_{10}	Singlet	**1025.68**	**2.563**	**102.846**
C_1,C_6	Triplet	1836.22	4.589	15.882
		1842.76	**4.605**	**30.268**
		1849.17	4.621	16.258

Figure A 27: ^{13}C-NMR of VIII



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8,C_{10}	1938.35	19.264	42.416
2	C_3,C_4	2602.63	25.865	69.986
3	C_2,C_5	2856.70	28.390	64.768
4	C_1,C_6	7455.38	74.092	58.869
5	C_7,C_9	21734.12	215.996	14.038

Figure A 28: Mass Spectrum of VIII



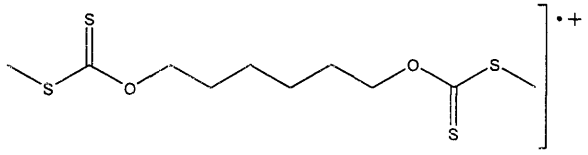
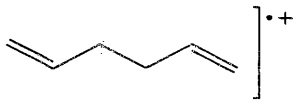
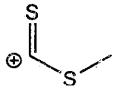
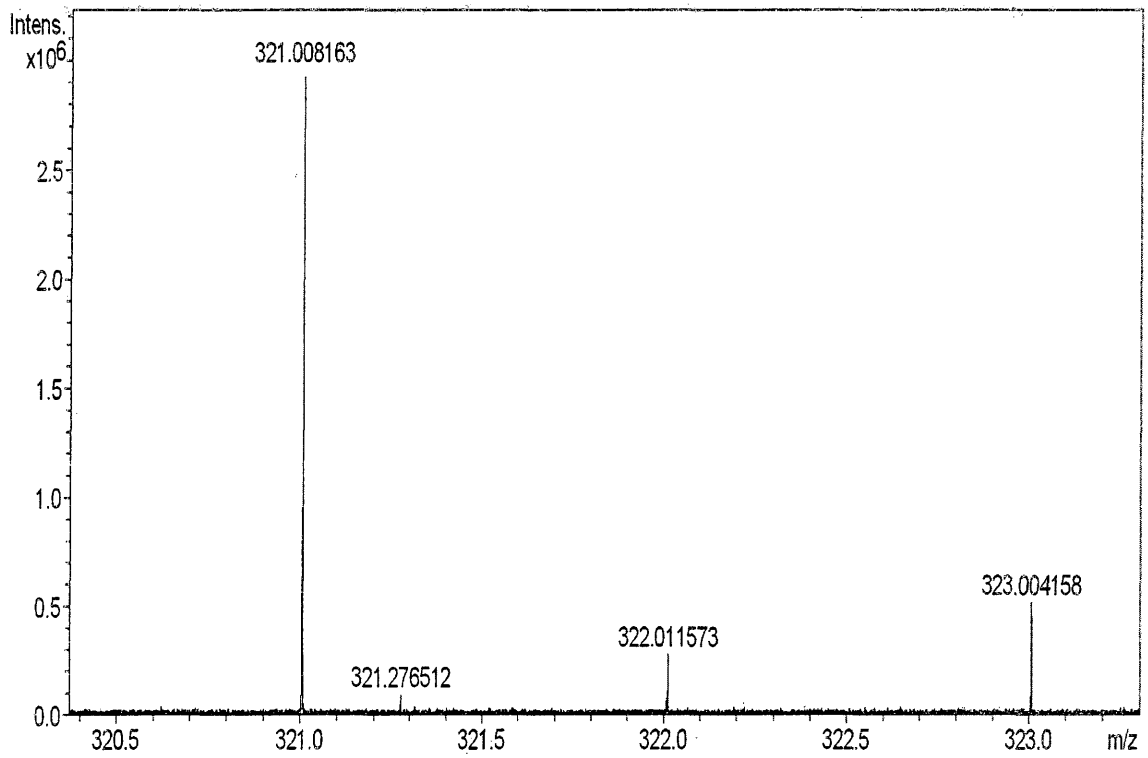
Mass	Ion / Radical	
208		Molecular Ion
82		
91		

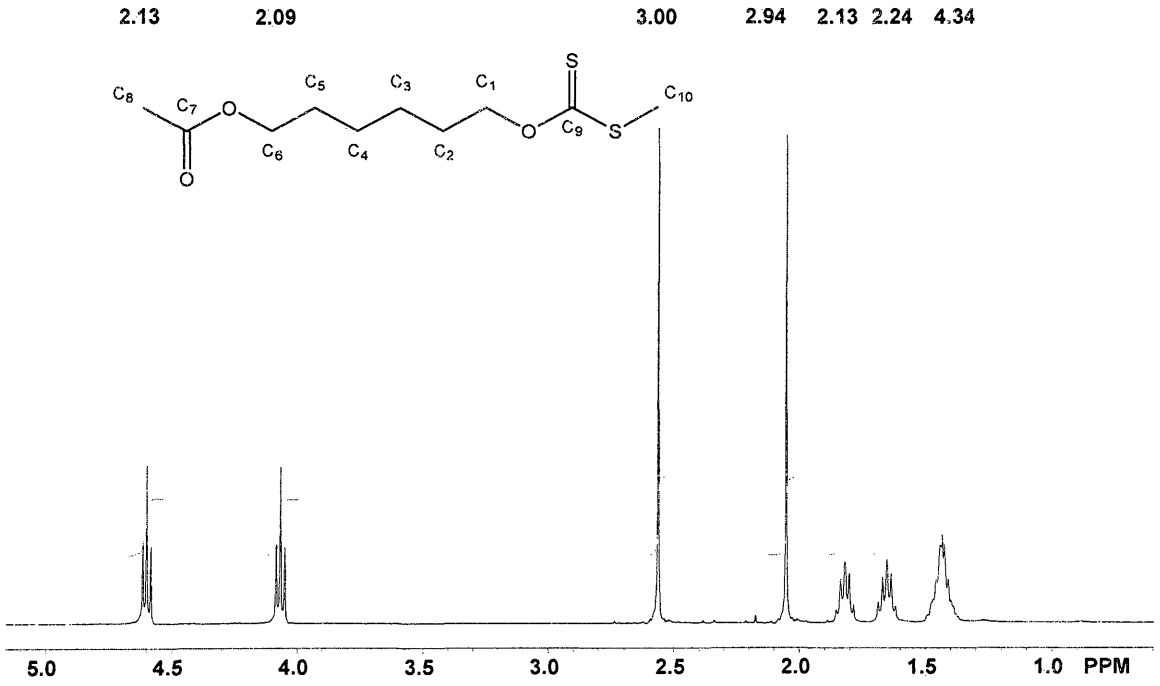
Figure A 29: Mass Spectrum of C10H18O2S4Na+



Exact mass of C10H18O2S4Na+ = 321.008184u
Observed mass: 321.008163u
Difference: <-1.0ppm

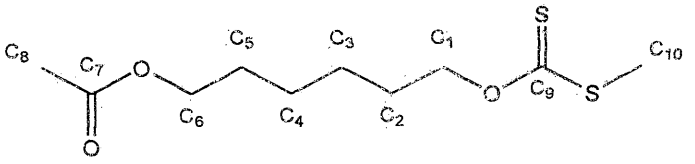
1:1 THF:MeOH with NaCl and analyzed by positive ion electrospray on a Bruker 12 Tesla APEX -Qe FTICR-MS with an Apollo II ion source

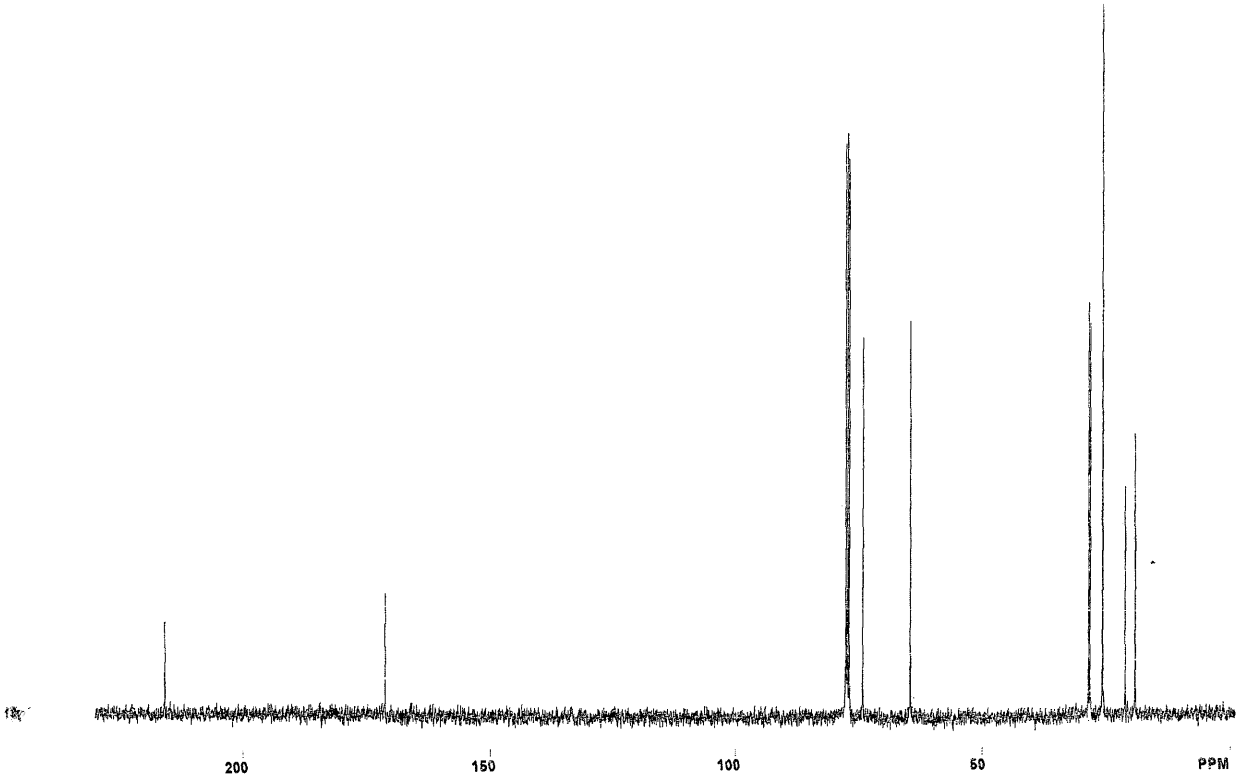
Figure A 30: ^{1}H-NMR of IX



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_3,C_4	Multiplet	**574.81**	**1.437**	**17.765**
C_5	Pentet	648.46	1.621	3.445
		655.13	1.637	10.072
		662.13	**1.655**	**12.848**
		669.15	1.672	9.317
		676.26	1.690	4.270
C_2	Pentet	714.72	1.786	3.686
		721.76	1.804	9.936
		728.84	**1.822**	**12.309**
		736.04	1.840	8.915
		742.60	1.856	2.667
C_8	Singlet	**821.54**	**2.053**	**101.497**
C_{10}	Singlet	**1025.51**	**2.563**	**102.737**
C_6	Triplet	1621.10	4.051	15.938
		1627.75	**4.068**	**32.612**
		1634.38	4.085	16.718
C_1	Triplet	1834.08	4.584	16.026
		1840.60	**4.600**	**32.576**
		1846.79	4.615	16.280

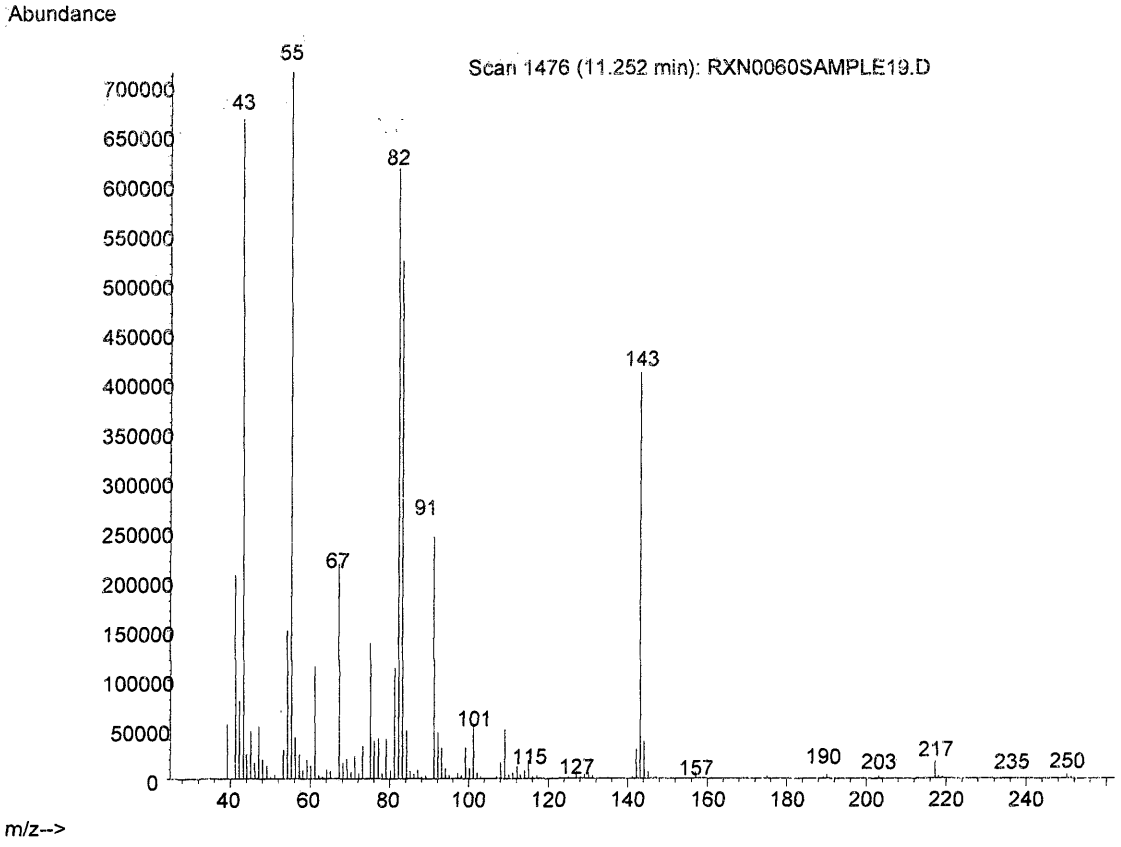
Figure A 31: ^{13}C-NMR of IX





Peak	Carbon	Hz	ppm	Relative Intensity
1	C_{10}	1941.50	19.295	36.464
2	C_8	2147.98	21.347	29.484
3	C_3,C_4	2608.67	25.925	101.561
4	C_5	2864.42	28.467	51.225
5	C_2	2896.65	28.787	53.944
6	C_6	6503.29	64.630	49.513
7	C_1	7466.53	74.203	48.450
8	C_7	17237.38	171.307	15.822
9	C_9	21740.02	216.055	11.860

Figure A 32: Mass Spectrum of IX



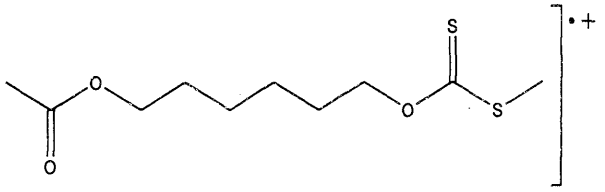
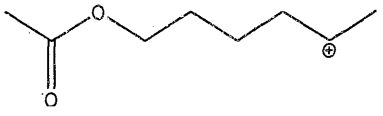
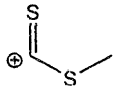
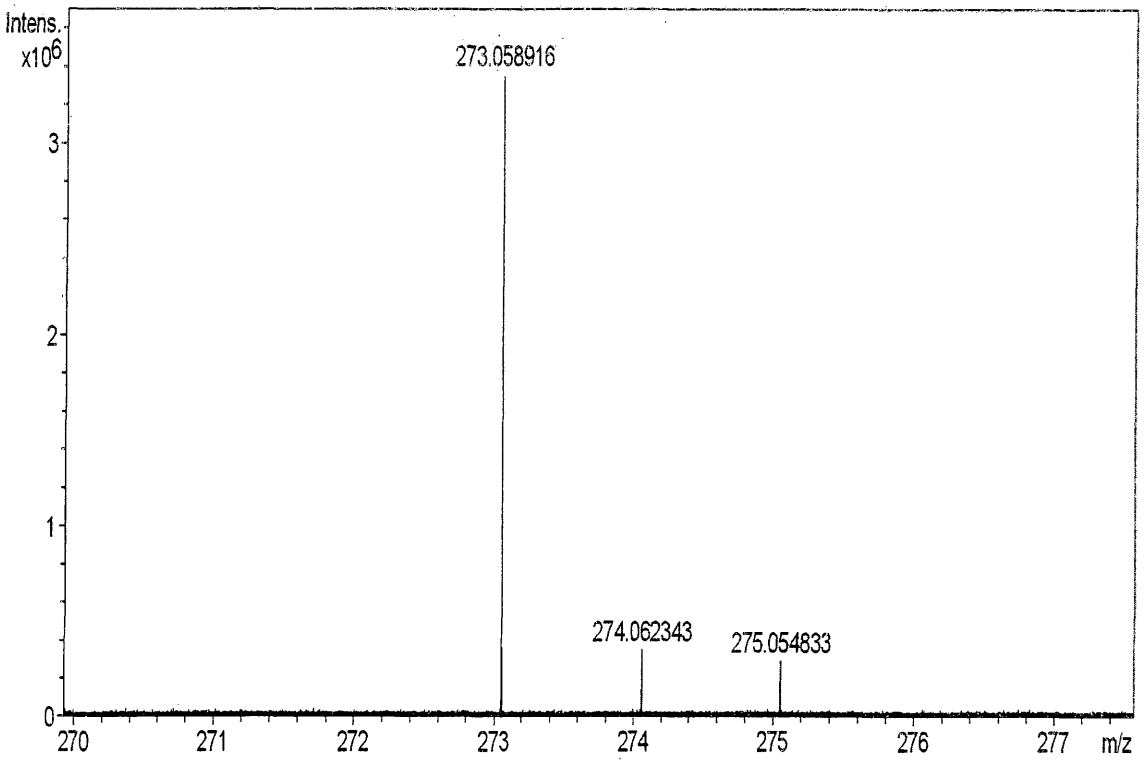
Mass	Ion / Radical	
250		Molecular Ion
143		
91		

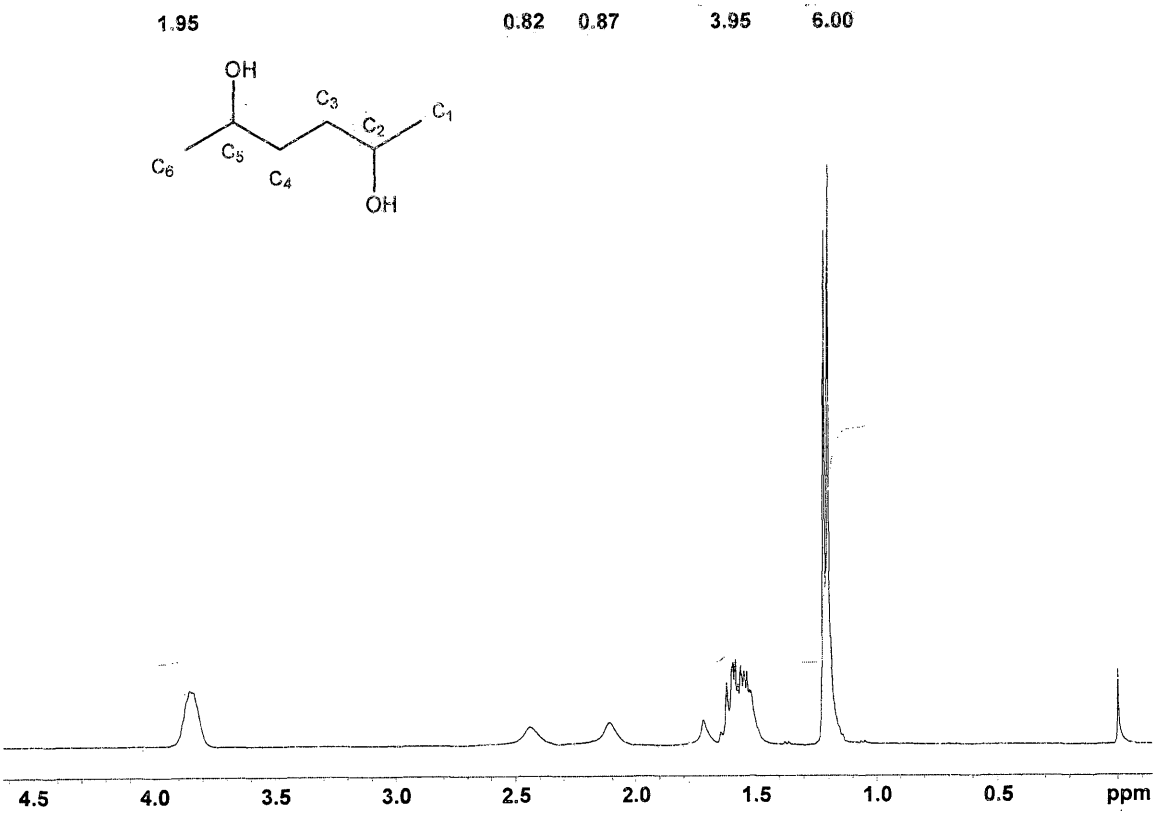
Figure A 33: Mass Spectrum of C10H18O3S2Na+



Exact mass of C10H18O3S2Na+ = 273.058957u
Observed mass: 273.058916u
Difference: <-1.0ppm

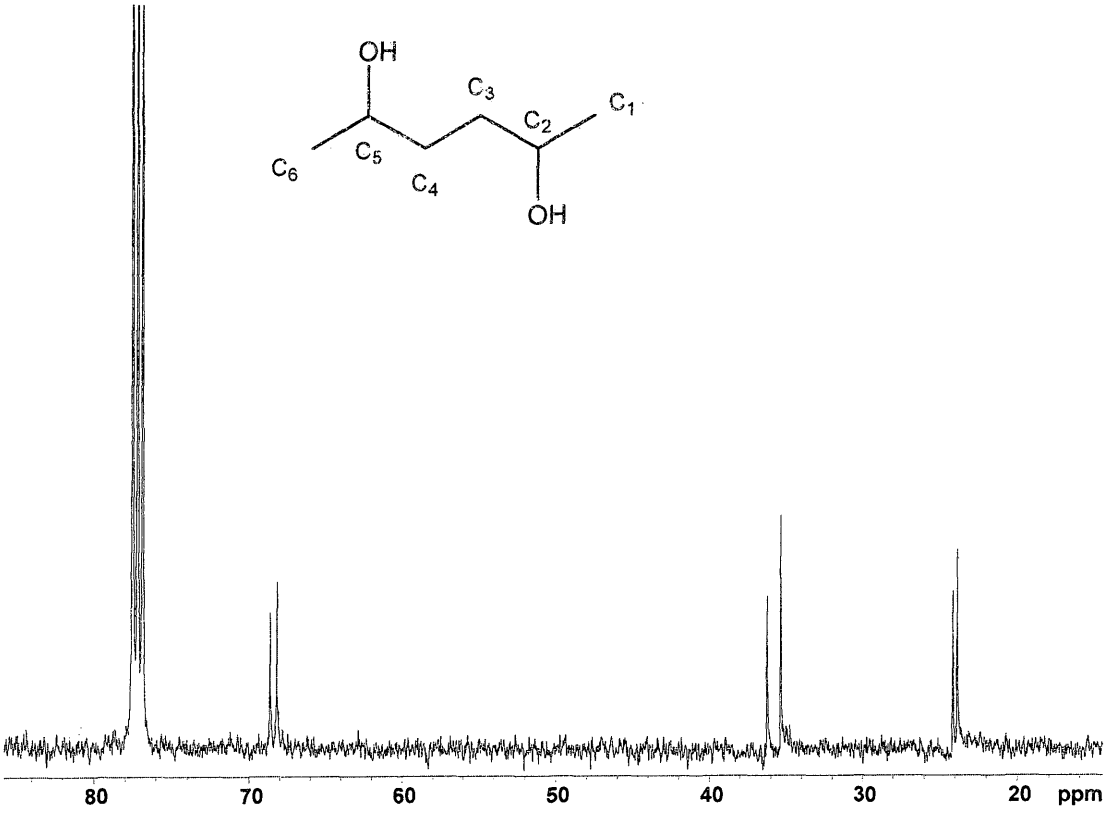
1:1 THF:MeOH with NaCl and analyzed by positive ion electrospray on a Bruker 12 Tesla APEX -Qe FTICR-MS with an Apollo II ion source

Figure A 34: ^{1}H-NMR of 2,5-Hexanediol (meso and enatiomeric mix)



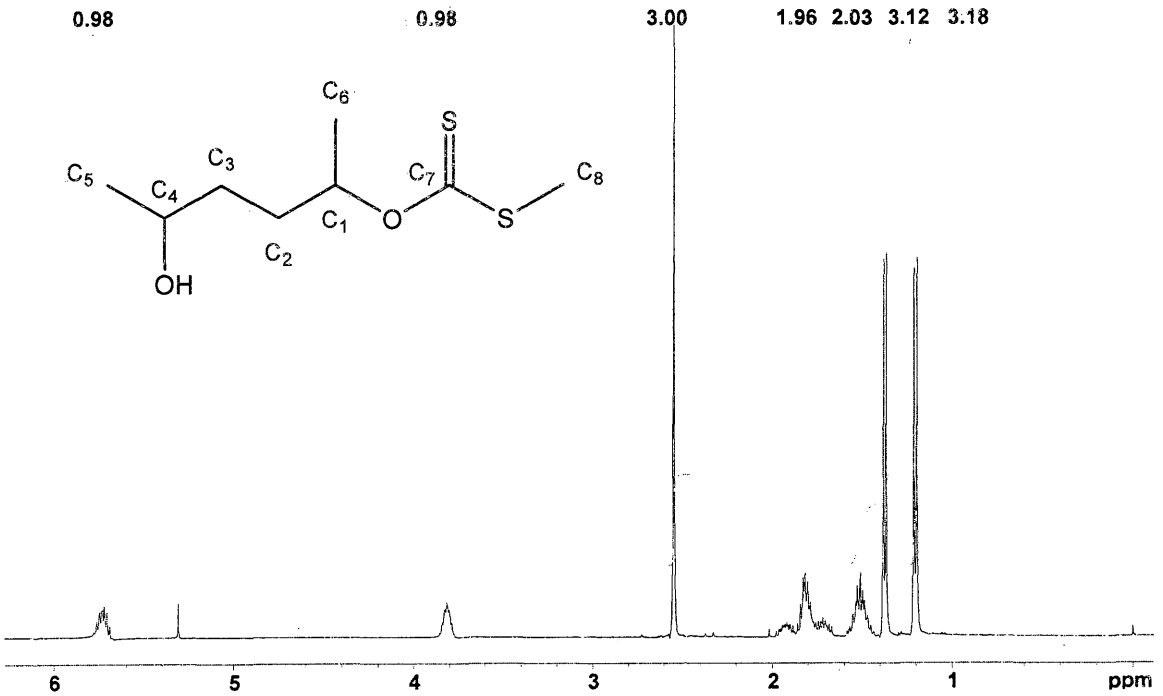
Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_1,C_6	Doublet	483.32	1.208	102.530
		489.77	1.224	88.443
C_3,C_4	Multiplet	607.74	1.519	9.251
		614.93	1.537	12.780
		619.17	1.547	12.683
		625.09	1.562	13.794
		648.63	1.621	10.902
	Singlet	845.02	2.112	3.897
Hydroxyl				
	Singlet	975.55	2.438	3.168
Hydroxyl				
C_2,C_5	Multiplet	1536.75	3.841	9.455
		1541.90	3.854	9.716

Figure A 35: ^{13}C-NMR of 2,5-Hexanediol (meso and enatiomeric mix)



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_1,C_6	2398.77	23.839	14.216
2	C_1,C_6	2429.17	24.141	10.930
3	C_3,C_4	3555.60	35.336	16.790
4	C_3,C_4	3644.34	36.218	10.507
5	C_2,C_5	6861.75	68.193	11.994
6	C_2,C_5	6907.86	68.651	9.667

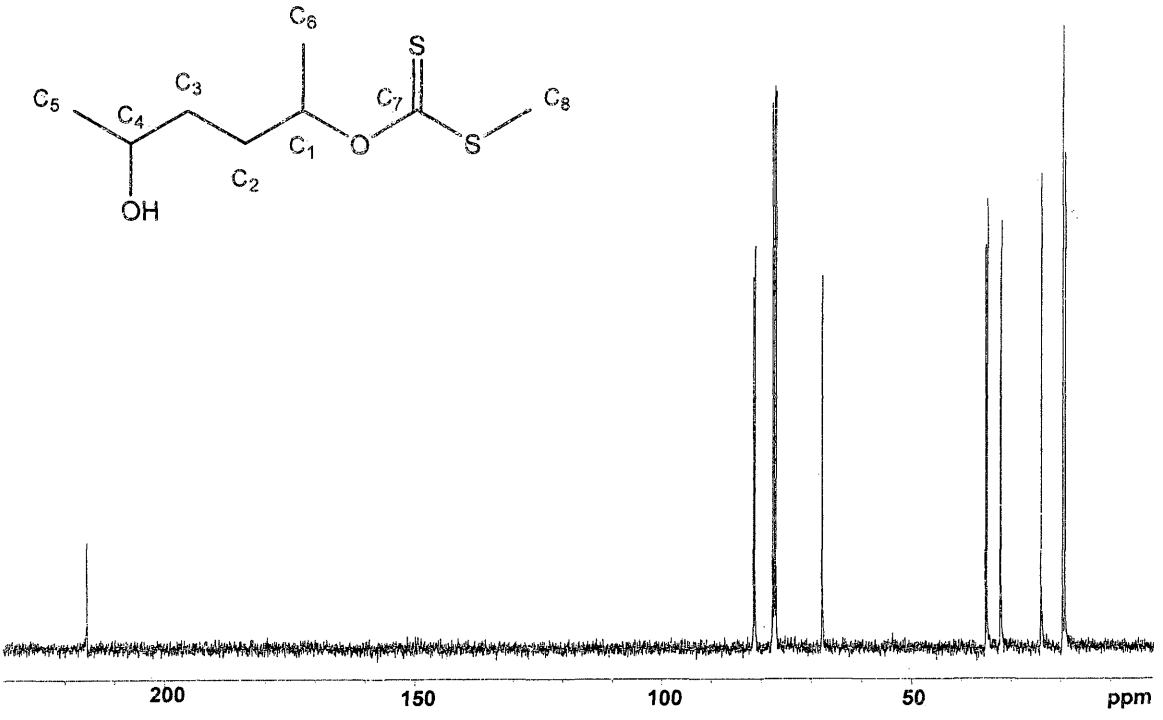
Figure A 36: ^{1}H-NMR of X



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_5	Doublet	**479.32**	**1.198**	**63.436**
		485.48	**1.213**	**63.747**
C_6	Doublet	**547.04**	**1.367**	**65.724**
		553.32	**1.383**	**65.203**
C_3	Multiplet	**604.00**	**1.510**	**10.585**
C_2	Mutiplet	**727.13**	**1.817**	**10.364**
C_8	Singlet	**1019.63**	**2.548**	**100.513**
C_4	Multiplet[a]	1509.82	3.773	0.547
		1515.80	3.788	2.420
		1521.74	3.803	4.541
		1526.74	**3.816**	**5.652**
		1531.35	3.827	4.546
		1537.78	3.843	2.550
		1544.23	3.859	0.691
C_1	Multiplet[a]	2270.02	5.673	0.204
		2276.21	5.689	1.985
		2282.93	5.706	4.352
		2289.17	**5.721**	**5.320**
		2294.00	5.733	4.642
		2299.32	5.746	4.271
		2305.52	5.762	2.674

[a]Multiplet shows unresolved splitting beyond septet

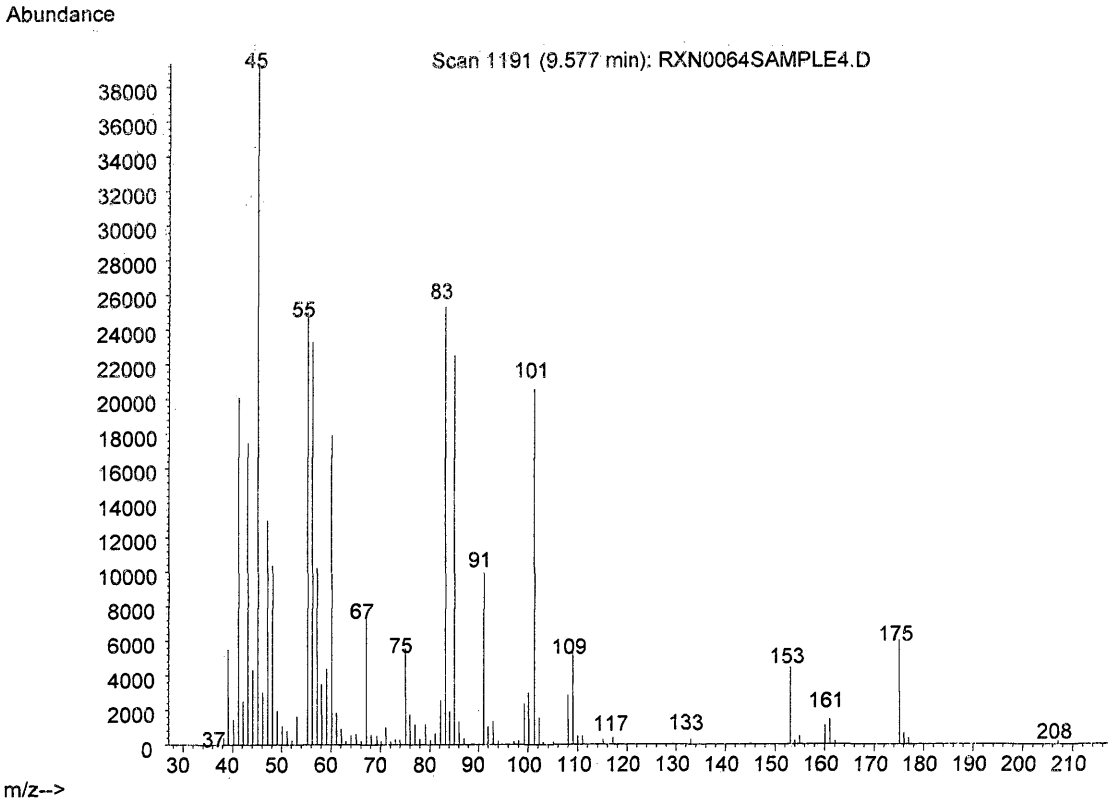
Figure A 37: ^{13}C-NMR of X



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1923.38	19.115	66.846
2	C_6	1973.51	19.613	102.366[a]
3	C_5	2402.25	23.874	60.827
4	C_5	2405.70	23.908	67.662
5	C_2	3220.67	32.007	57.625
6	C_2	3235.92	32.159	51.222
7	C_3	3501.45	34.798	60.913
8	C_3	3526.82	35.050	54.096
9	C_4	6819.33	67.771	51.343
10	C_4	6827.62	67.854	47.348
11	C_1	8172.12	81.215	57.094
12	C_1	8198.93	81.482	53.185
13	C_7	21685.90	215.517	13.681
14	C_7	21689.81	215.556	14.073

[a]Peak integrates for 2 carbons due to overlap of diastereometric carbons

Figure A 38: Mass Spectrum of X



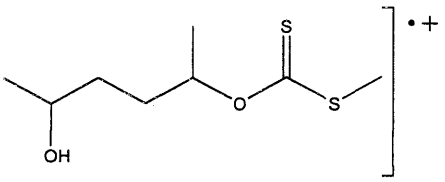
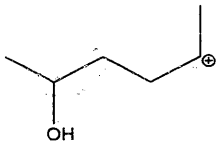
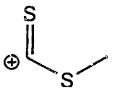
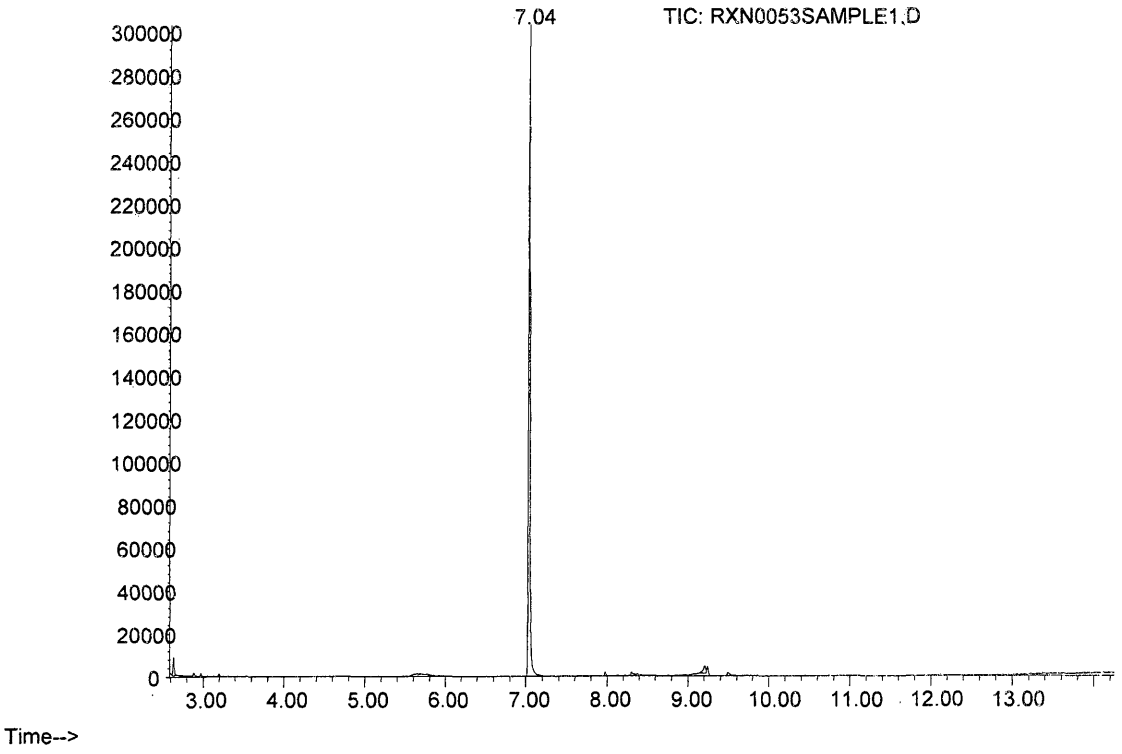
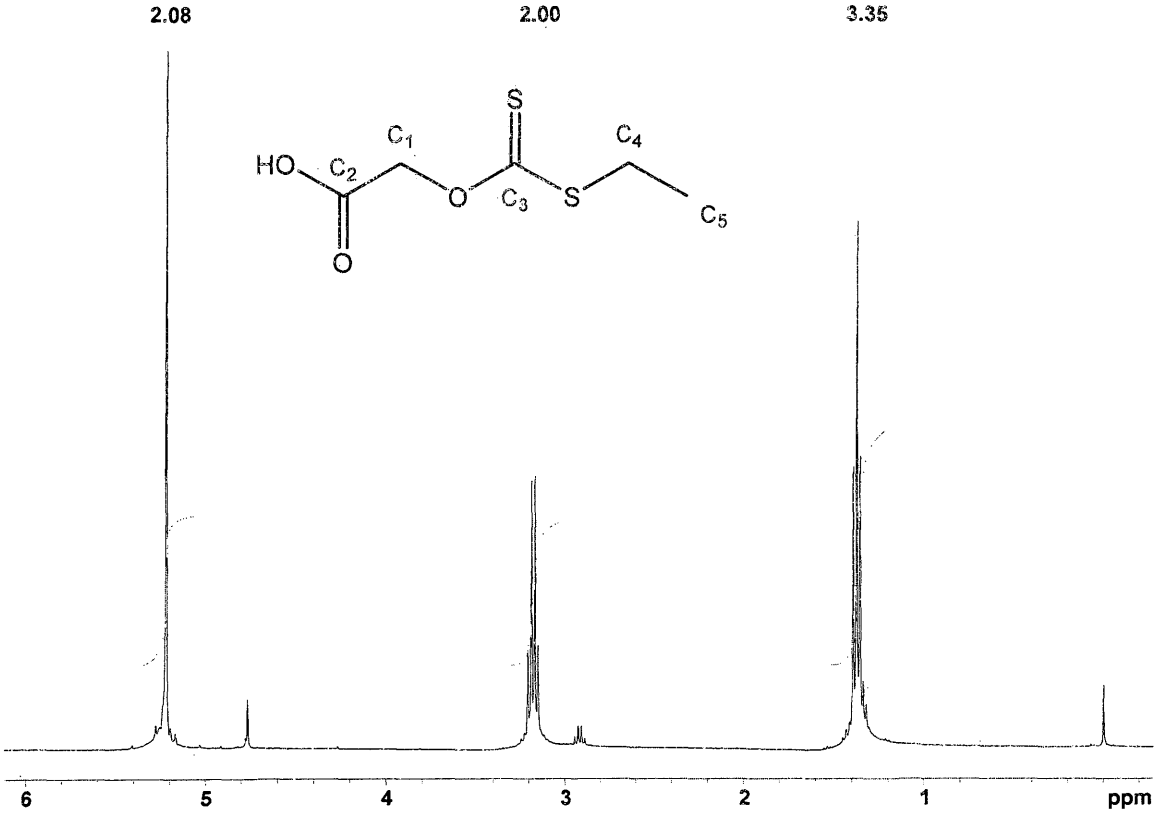
Mass	Ion / Radical	
180		Molecular Ion
101		
91		

Figure A 39: Gas Chromatograph from Failed Synthesis of X



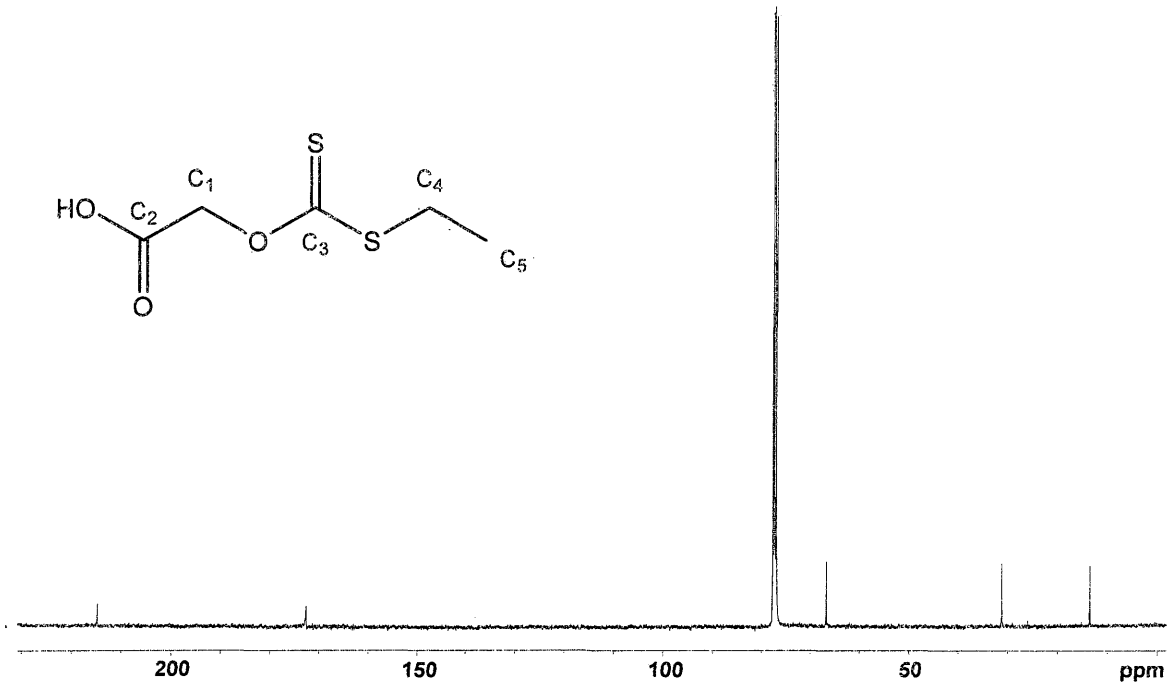
Retention time (min)	**Name**
7.04	Dimethyltrithiocarbonate

Figure A 40: ^{1}H-NMR of XI



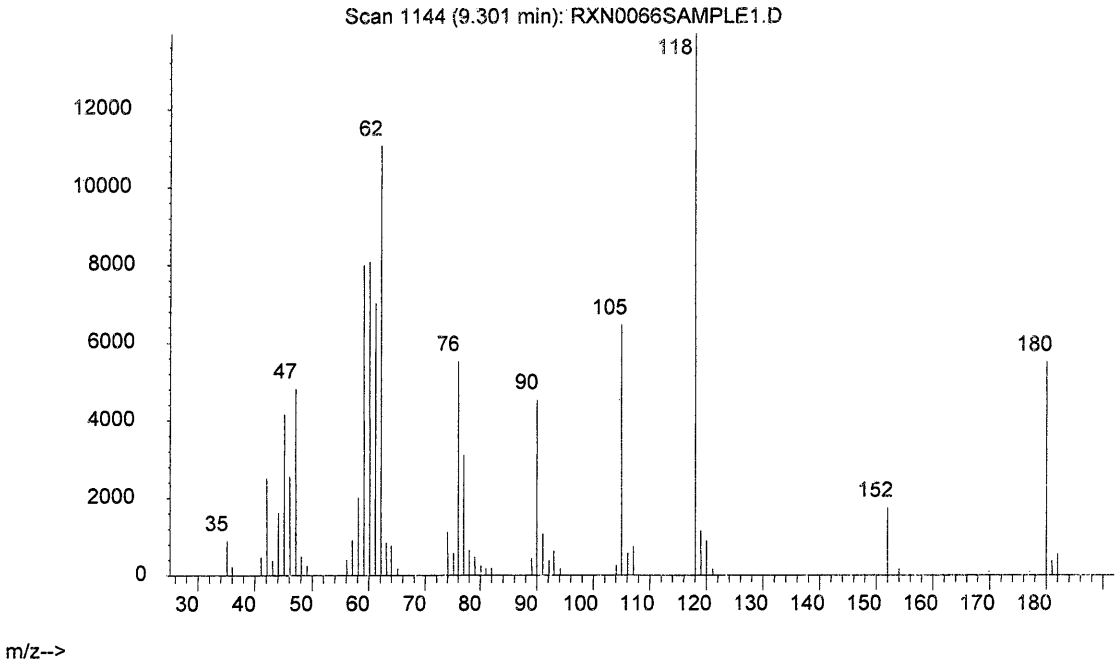
Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_5	Triplet	543.85	1.359	41.810
		551.22	**1.378**	**75.810**
		558.62	1.396	40.489
C_4	Quartet	1260.64	3.151	14.819
		1268.10	**3.169**	**39.661**
		1275.53	**3.188**	**39.053**
		1282.96	3.206	14.335
C_1	Singlet	**2089.55**	**5.222**	**100.878**

Figure A 41: ^{13}C-NMR of XI



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_5	1353.65	13.453	9.910
2	C_4	3131.72	31.123	9.990
3	C_1	6714.07	66.725	10.513
4	C_2	17363.14	172.557	3.062
5	C_3	21609.49	214.757	3.445

Figure A 42: Mass Spectrum of XI



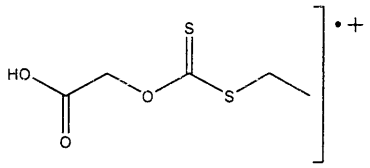
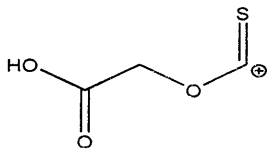
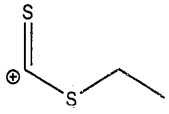
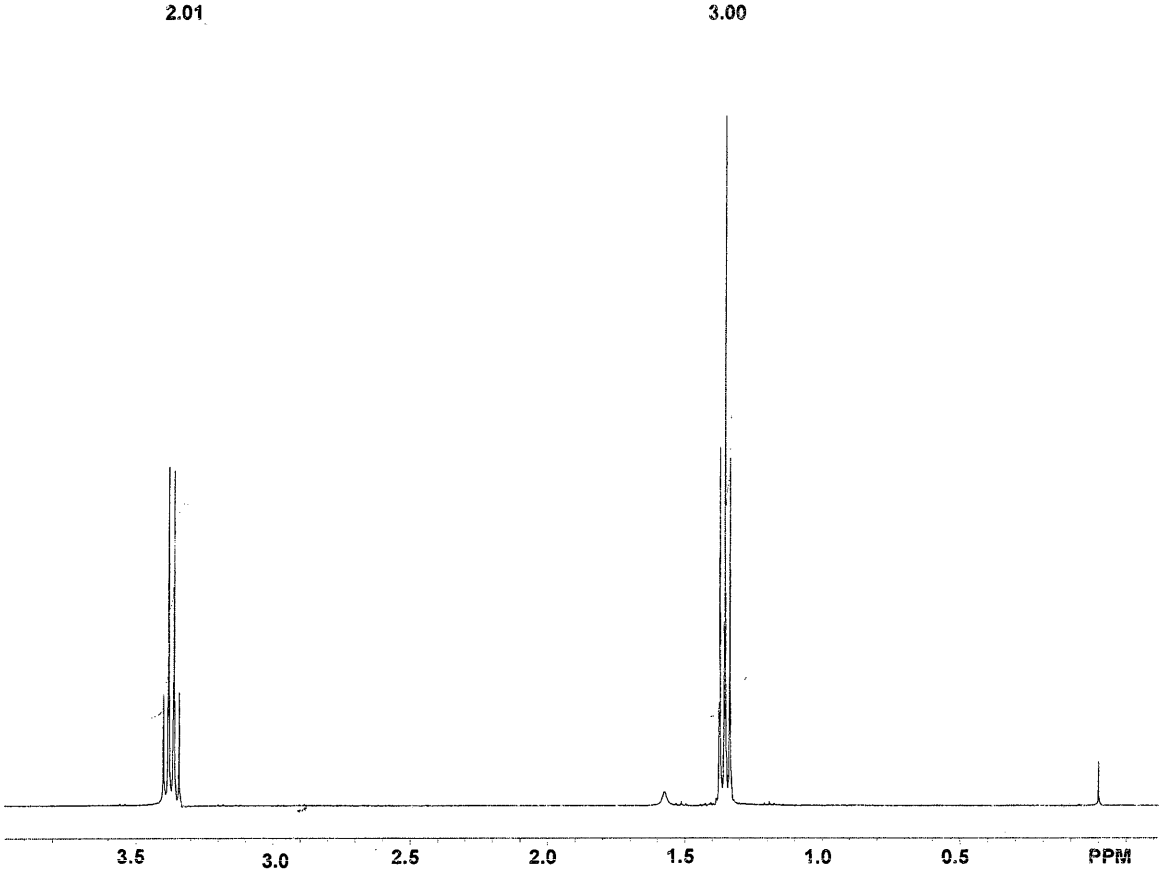
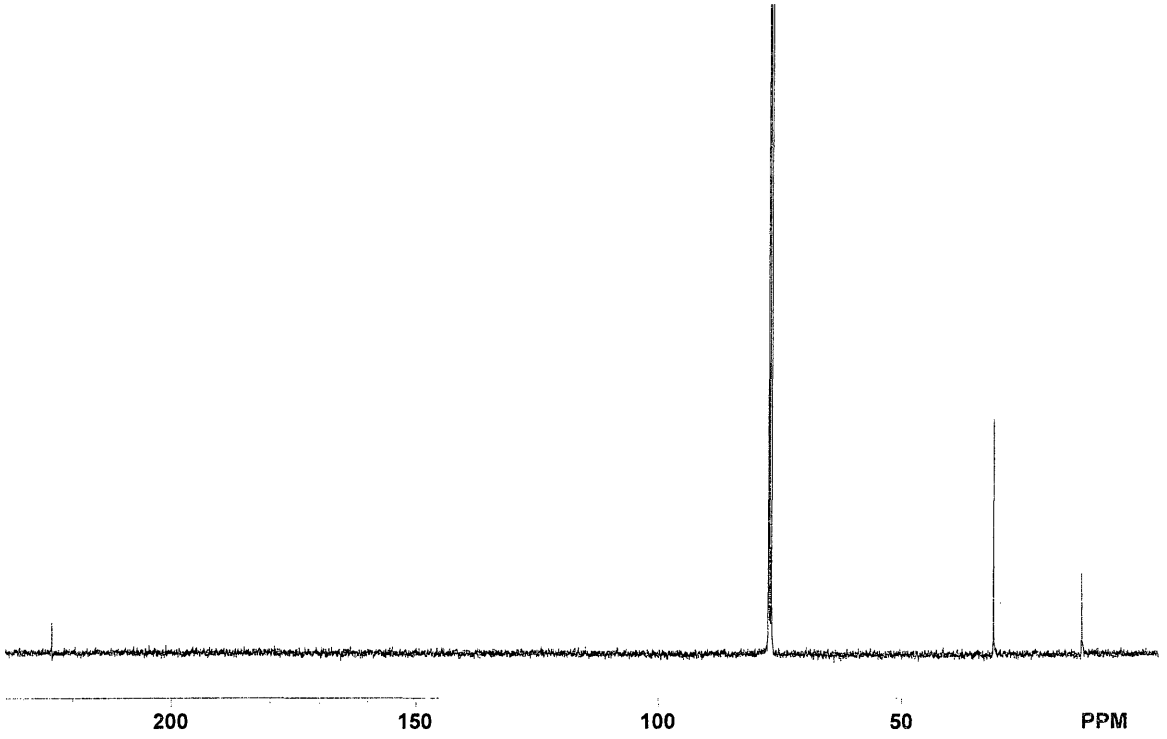
Mass	Ion / Radical	
180		Molecular Ion
118		
105		

Figure A 43: ^{1}H-NMR of Diethyltrithiocorbonate



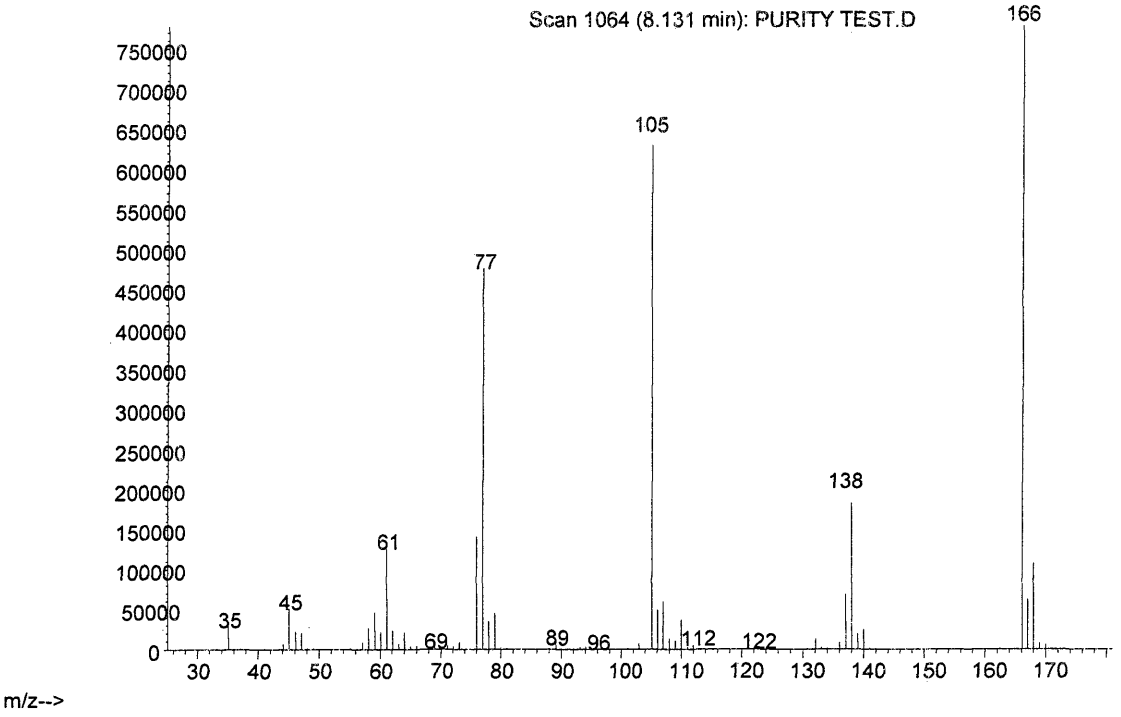
Parent Carbon	Multiplicty	Hz	ppm	Relative Intensity
C_2	Triplet	534.69	1.336	55.939
		542.11	**1.355**	**107.644**
		549.53	1.373	55.404
C_1	Quartet	1338.06	3.344	16.395
		1345.09	**3.362**	**48.894**
		1352.54	**3.380**	**50.723**
		1360.33	3.400	16.044

Figure A 44: ^{13}C-NMR of Diethyltrithiocorbonate



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_2	1345.98	13.376	44.558
2	C_1	3153.20	31.337	40.918
3	C_3	22593.29	224.535	0.603

Figure A 45: Mass Spectrum of Diethyltrithiocorbonate



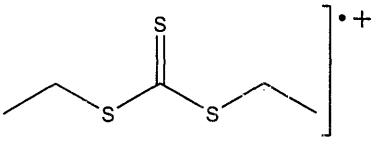
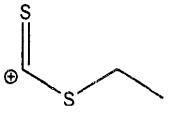
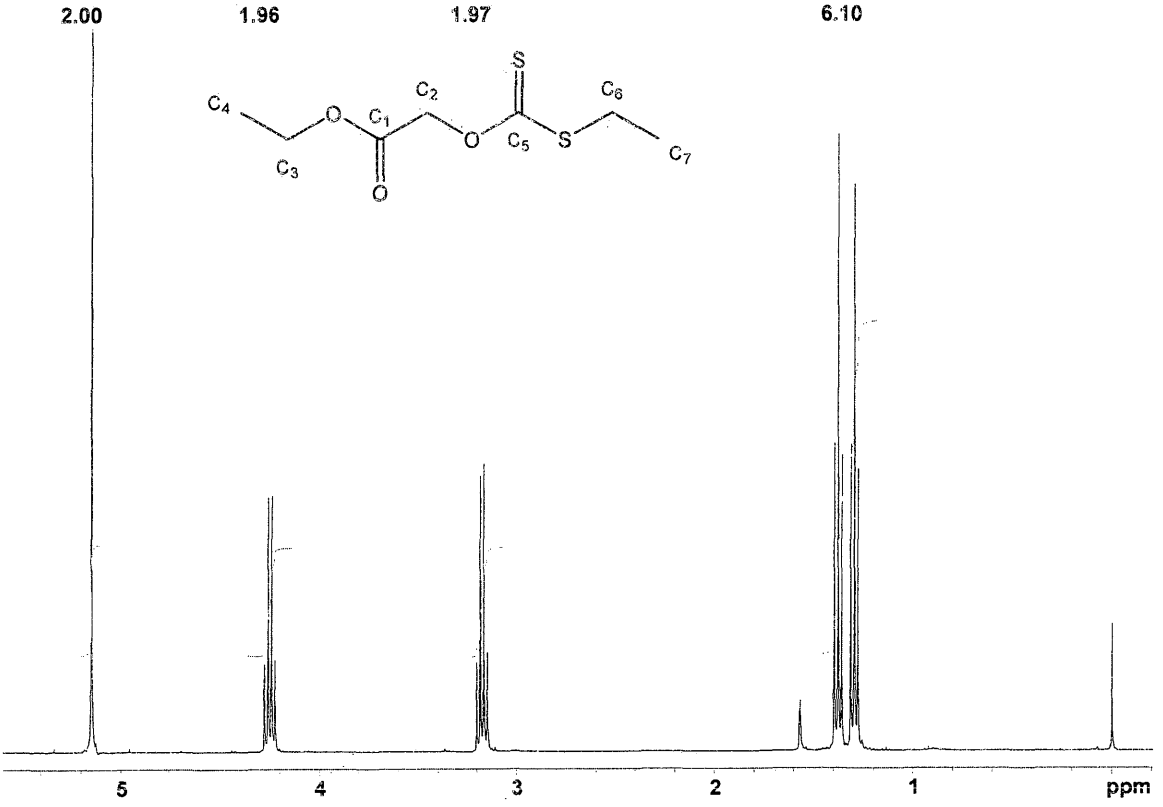
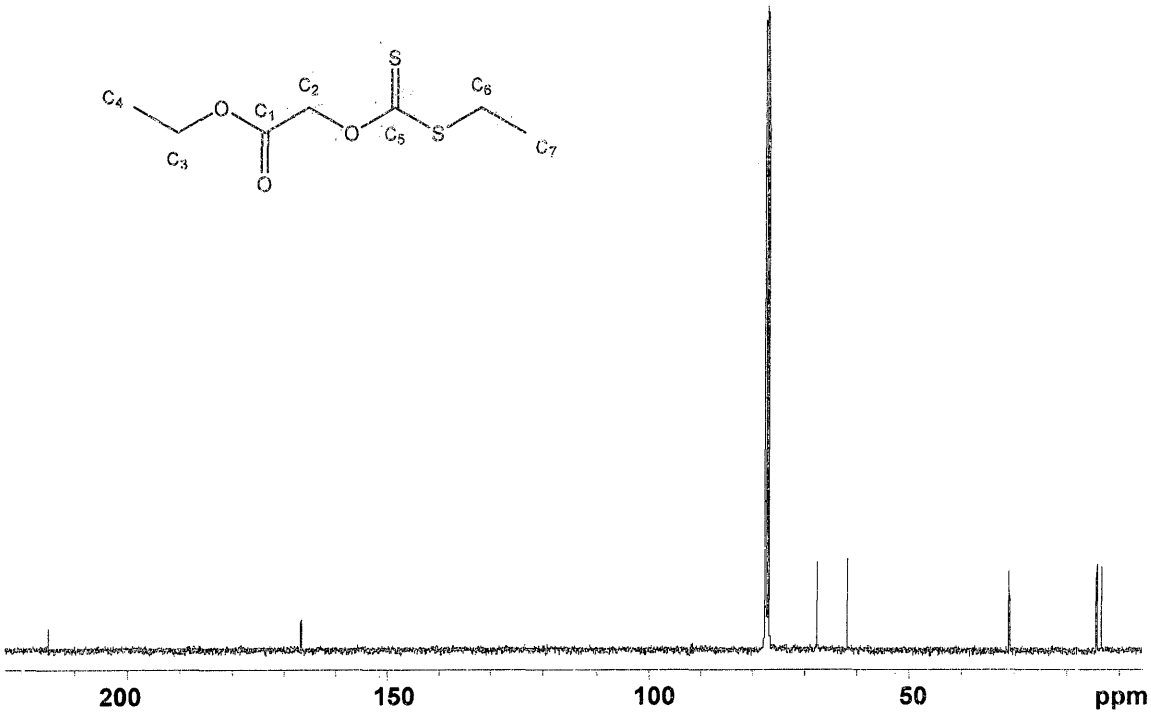
Mass	Ion / Radical	
166		Molecular Ion
105		

Figure A 46: ^{1}H-NMR of XII



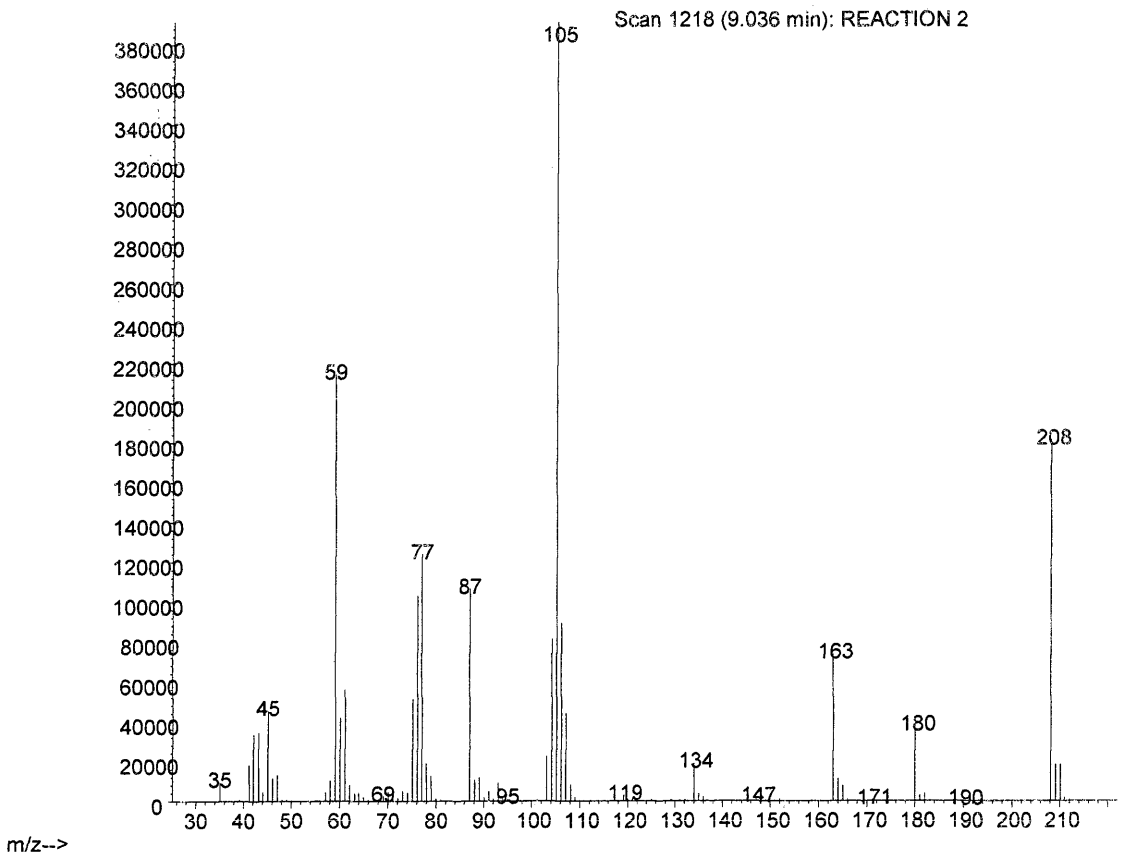
Parent Carbon	Multiplicity	Hz	ppm	Relative Intensity
C_4	Triplet	511.41	1.278	43.522
		518.79	**1.297**	**80.684**
		526.02	1.315	43.808
C_7	Triplet	544.47	1.361	40.773
		551.87	**1.379**	**85.831**
		559.28	1.398	42.446
C_6	Quartet	1259.35	3.147	14.625
		1266.75	**3.166**	**41.670**
		1274.16	**3.184**	**39.653**
		1281.59	3.203	12.486
C_3	Quartet	1691.34	4.227	13.033
		1698.16	**4.244**	**37.312**
		1705.54	**4.262**	**35.504**
		1712.78	4.281	12.287
C_2	Singlet	**2060.08**	**5.149**	**109.361**

Figure A 47: ^{13}C-NMR of XII



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_4	1368.08	13.596	12.212
2	C_7	1454.00	14.450	12.591
3	C_6	3119.85	31.005	12.046
4	C_3	6228.55	61.900	13.764
5	C_2	6812.88	67.707	13.900
6	C_1	16779.20	166.754	3.866
7	C_5	21627.85	214.940	1.951

Figure A 48: Mass Spectrum of XII



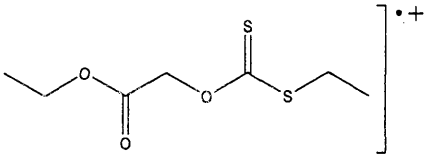
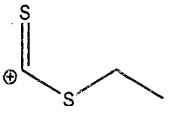
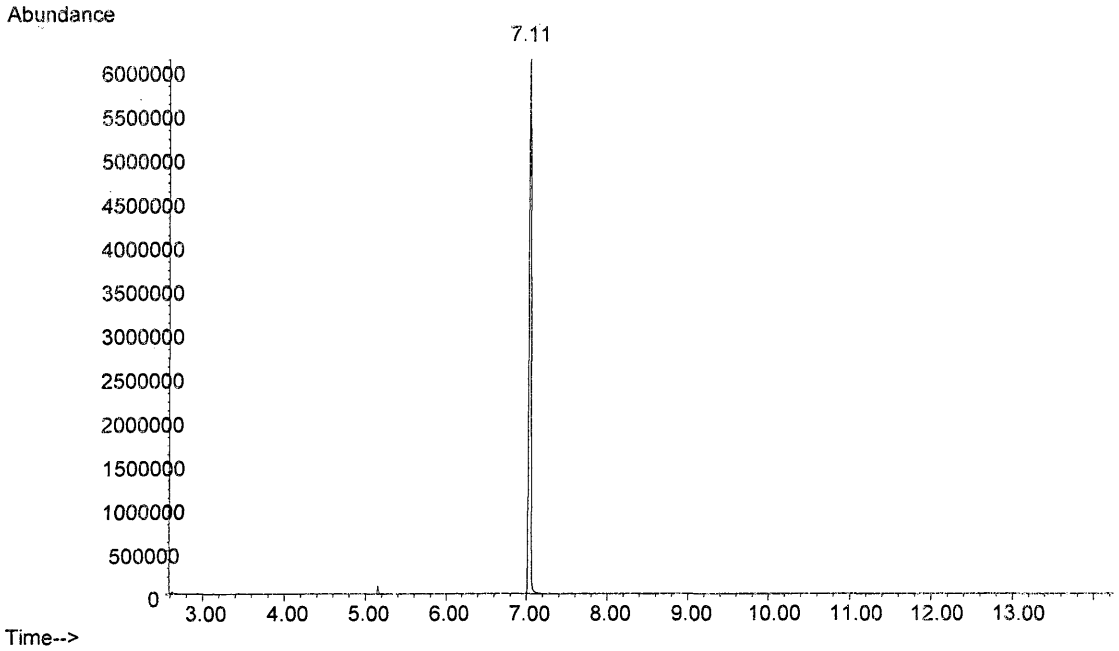
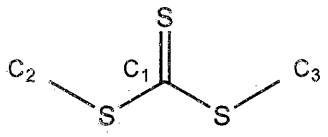
Mass	Ion / Radical	
208		Molecular Ion
105		

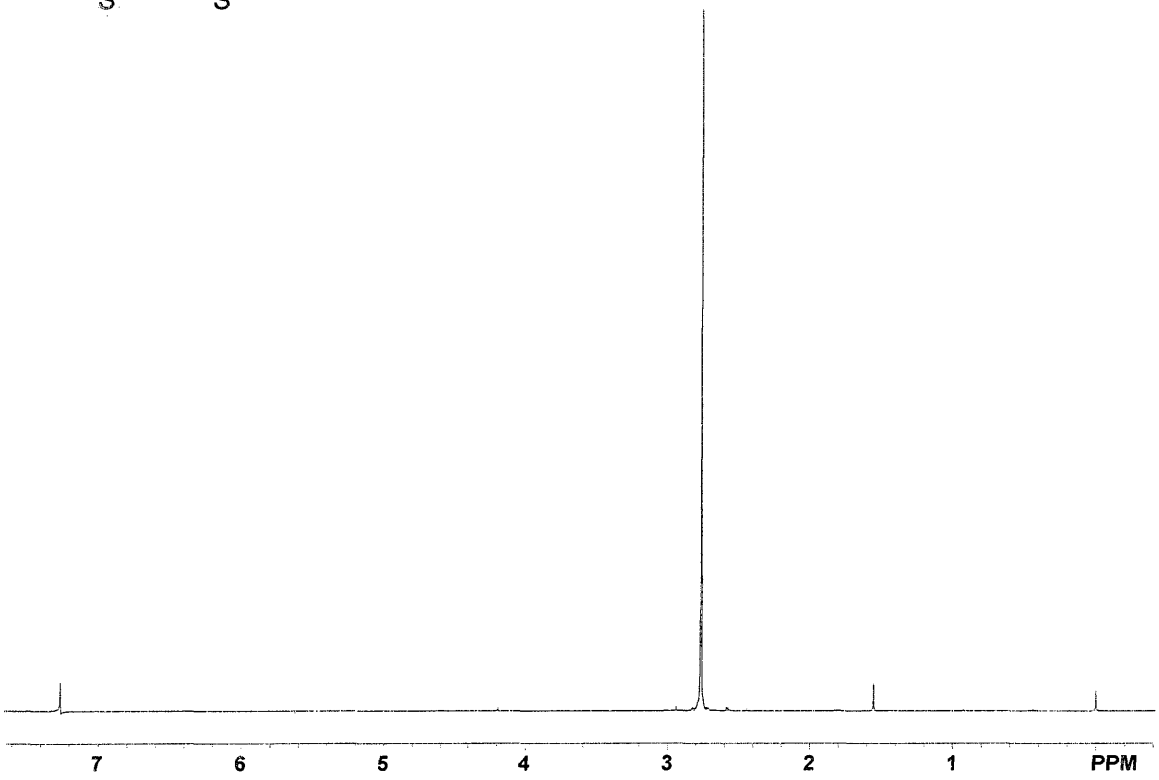
Figure A 49: Gas Chromatograph of Dimethyltrithiocarbonate



Retention time (min)	**Compound**
7.11	Dimethyltrithiocarbonate

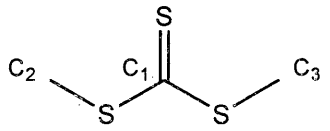
Figure A 50: ^{1}H-NMR of Dimethyltrithiocarbonate

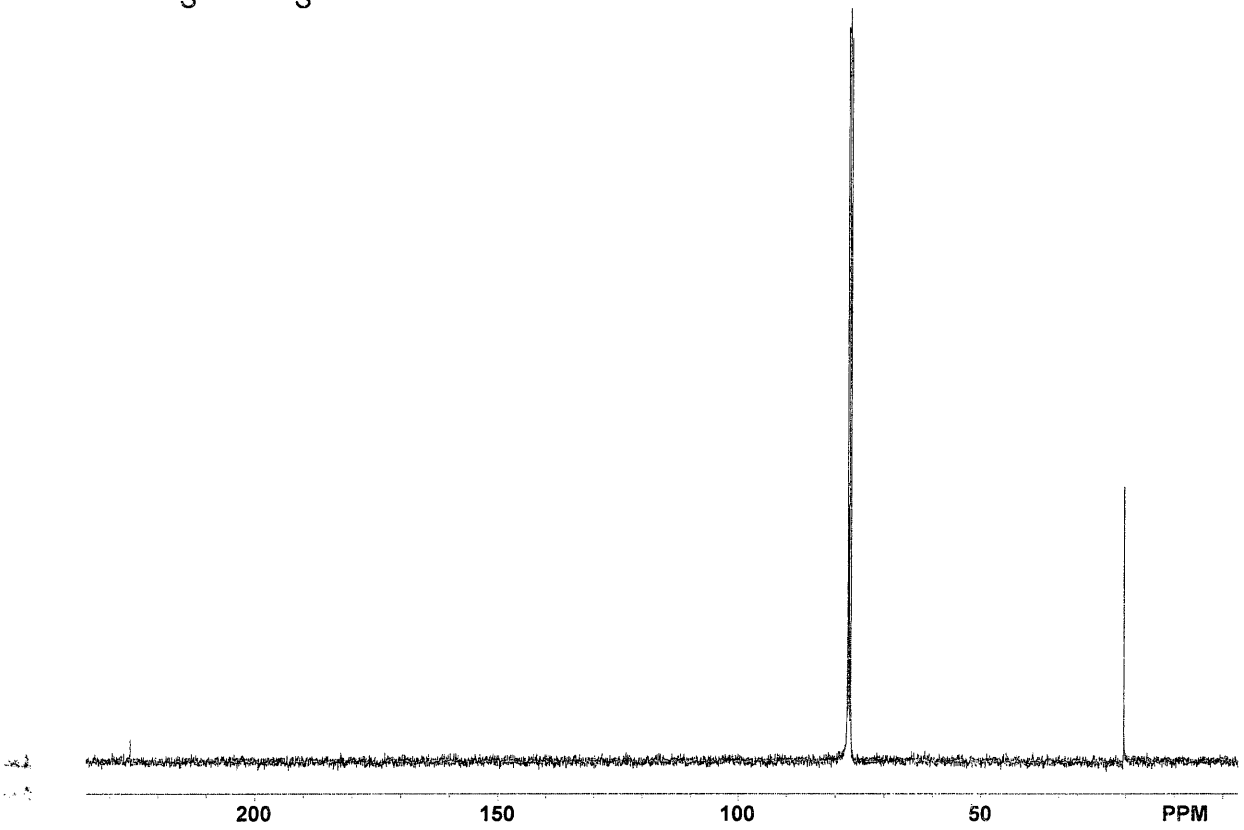




Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_2,C_3	Singlet	1105.95	2.764	101.528

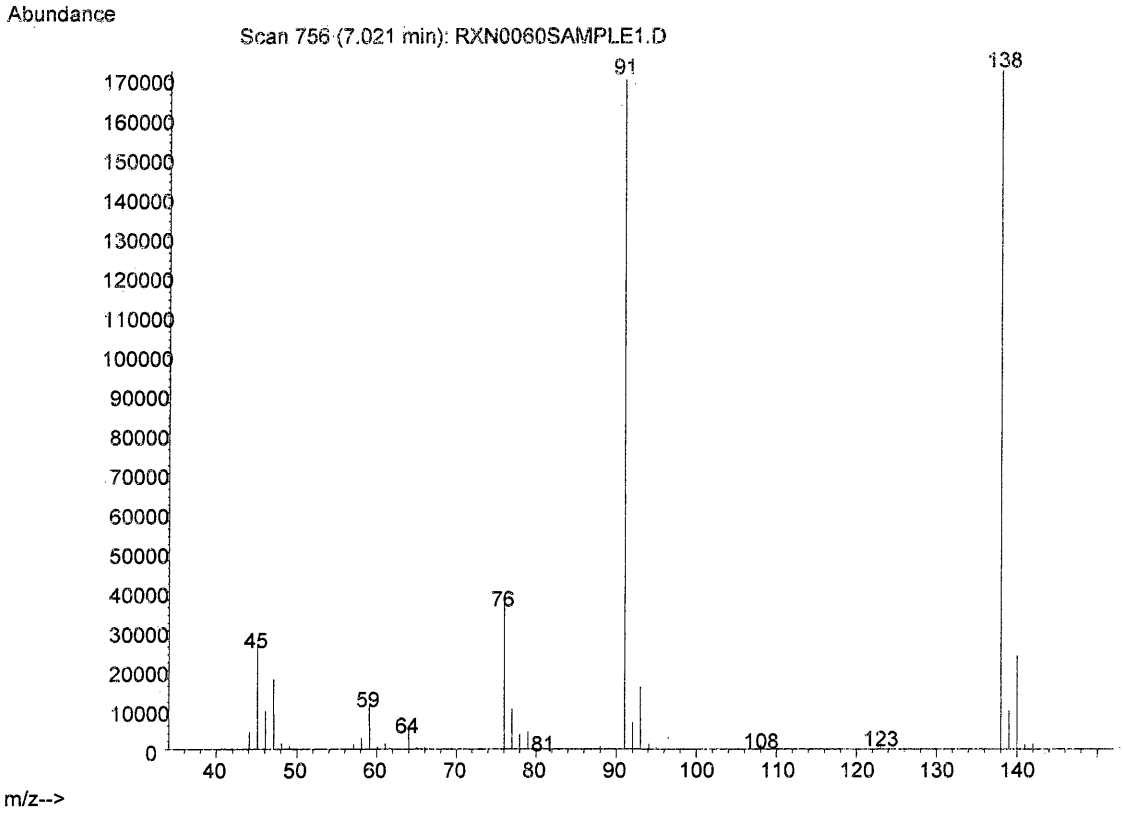
Figure A 51: ^{13}C-NMR of Dimethyltrithiocarbonate





Peak	Carbon	Hz	ppm	Relative Intensity
1	C_2,C_3	2059.45	20.467	37.753
2	C_1	22737.19	225.965	0.749

Figure A 52: Mass Spectrum of Dimethyltrithiocarbonate



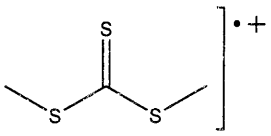
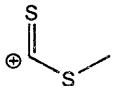
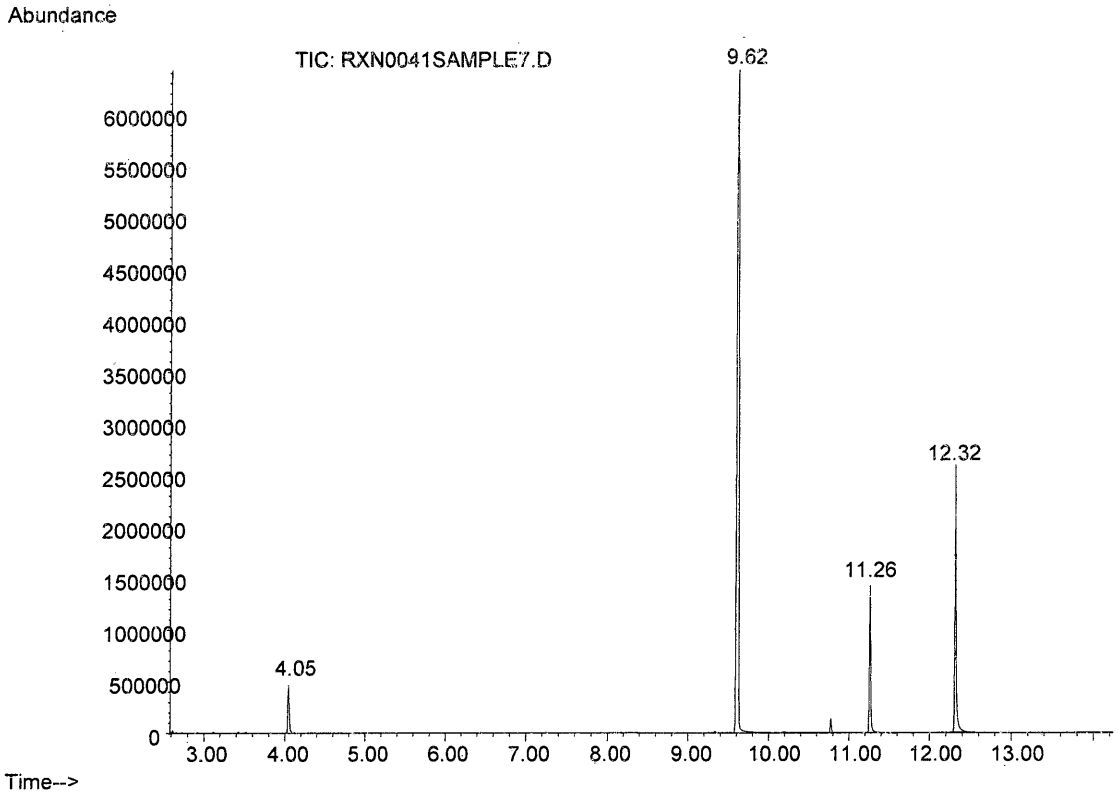
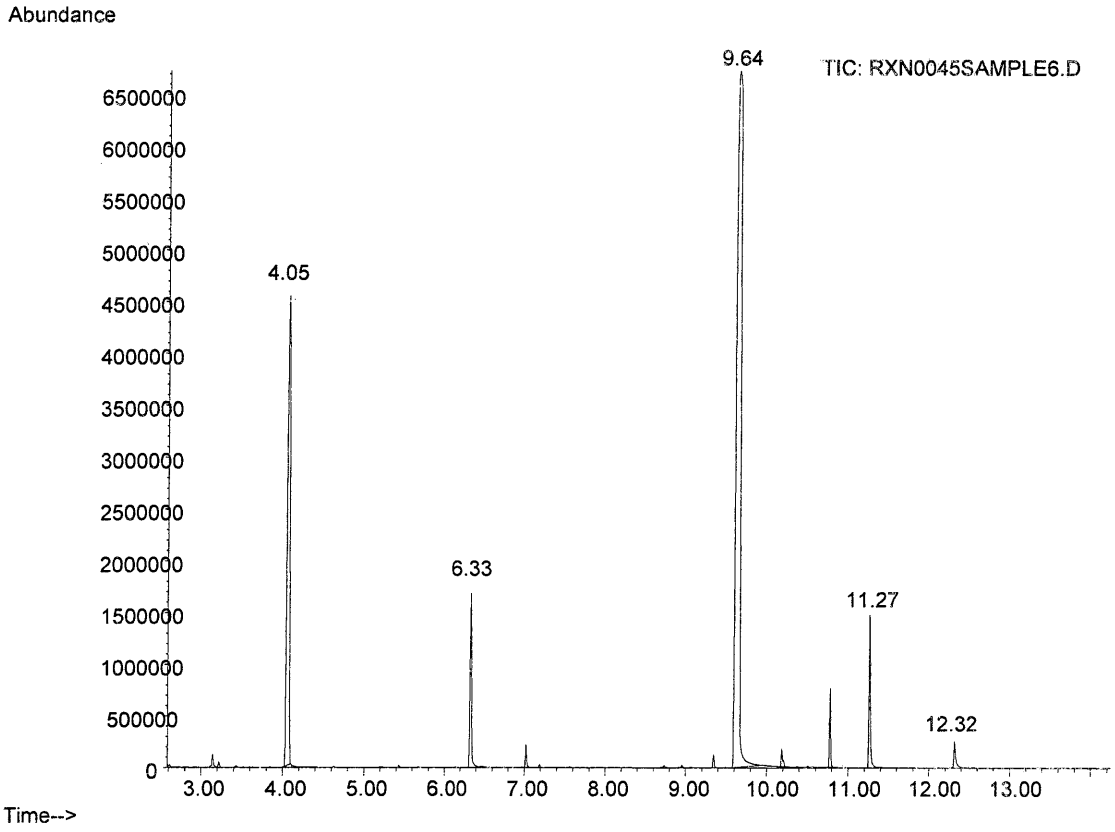
Mass	Ion / Radical	
138		Molecular Ion
91		

Figure A 53: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate I



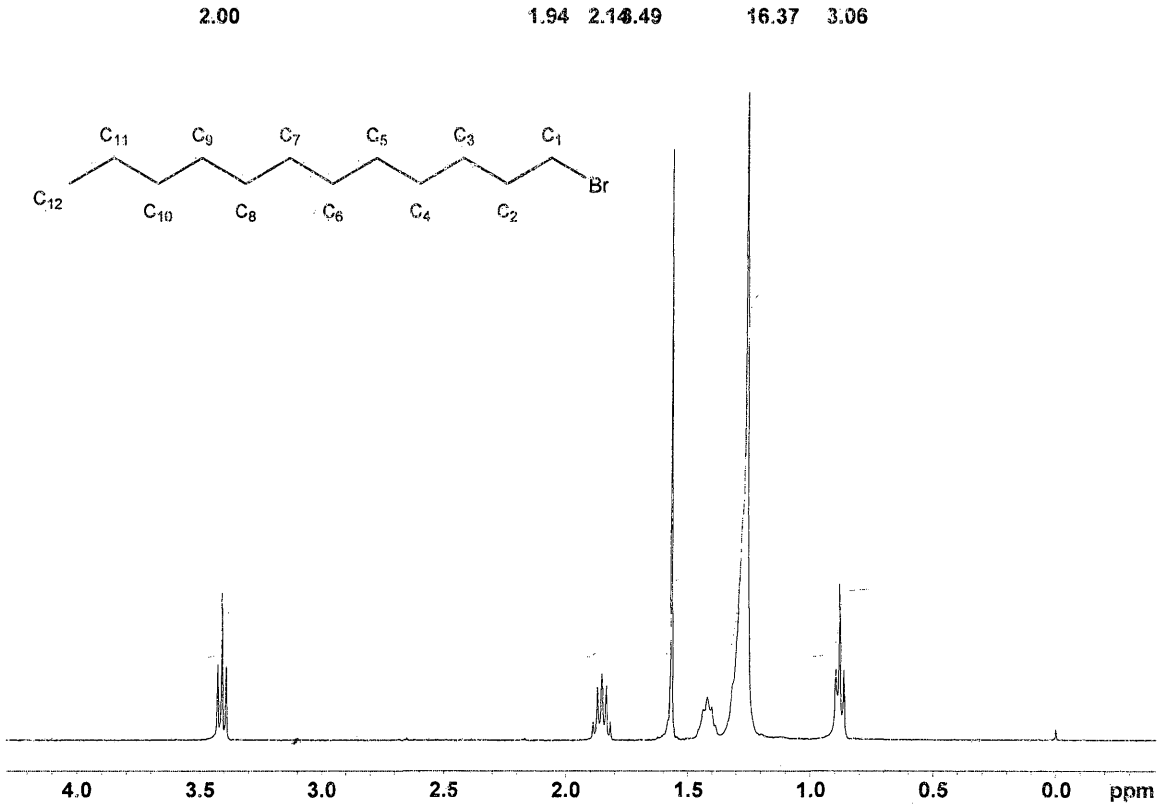
Retention time (min)	**Name**
4.05	Methyl bromothiolformate
9.62	1-Bromododecane
11.26	*O*-dodecyl-*S*-methylthiocarbonate
12.32	*O*-dodecyl-*S*-methylxanthate

Figure A 54: Gas Chromatograph of 2.0 Vilsmeier Equivalent Deprotection of Xanthate I



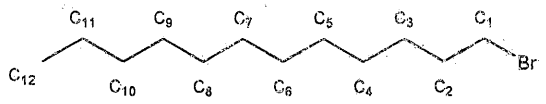
Retention time (min)	**Name**
4.05	Methyl bromothiolformate
6.33	4-Formylmorpholine
9.62	1-Bromododecane
11.26	*O*-dodecyl-*S*-methylthiocarbonate
12.32	*O*-dodecyl-*S*-methylxanthate

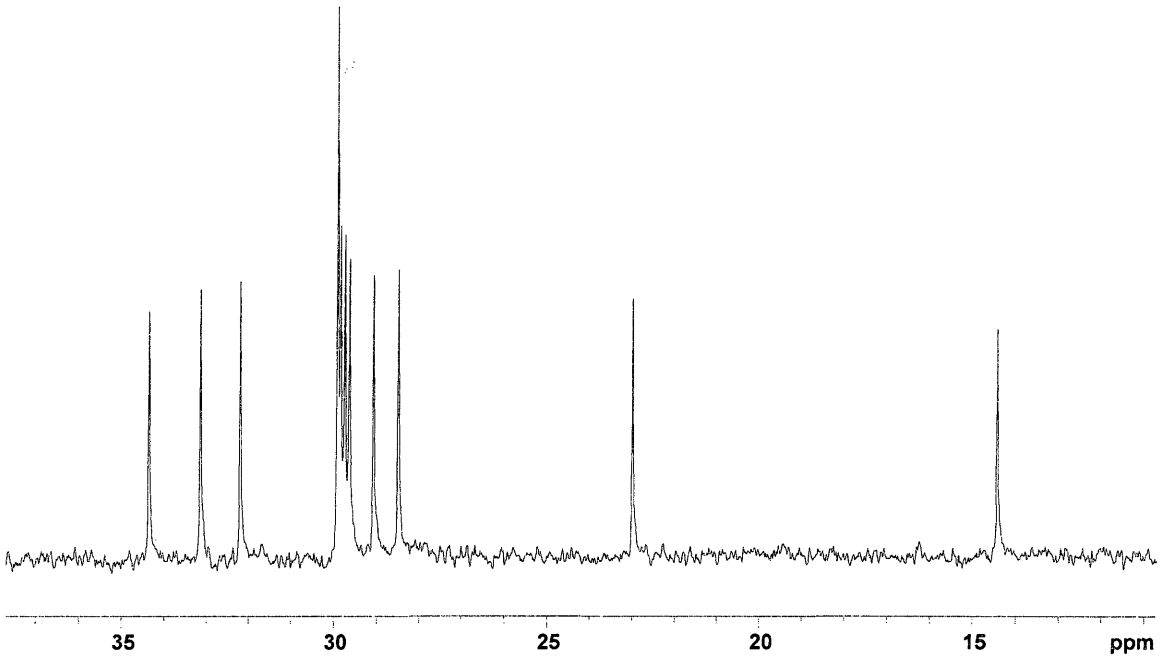
Figure A 55: ^{1}H-NMR of 1-Bromododecane



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_{12}	Triplet	345.61	0.864	10.280
		352.97	**0.882**	**19.712**
		358.74	0.897	10.291
C_3-C_{10}	Multiplet	**504.70**	**1.261**	**100.097**
C_{11}	Pentet	551.58	1.379	2.298
		558.62	1.396	5.088
		565.58	**1.413**	**6.649**
		572.19	1.430	4.850
		579.83	1.449	2.142
C_2	Pentet	727.03	1.817	2.807
		734.22	1.835	8.433
		741.72	**1.854**	**10.162**
		748.91	1.872	8.307
		755.88	1.889	2.791
C_1	Triplet	1356.71	3.391	8.460
		1363.58	**3.408**	**15.801**
		1370.57	3.425	8.455

Figure A 56: ^{13}C-NMR of 1-Bromododecane

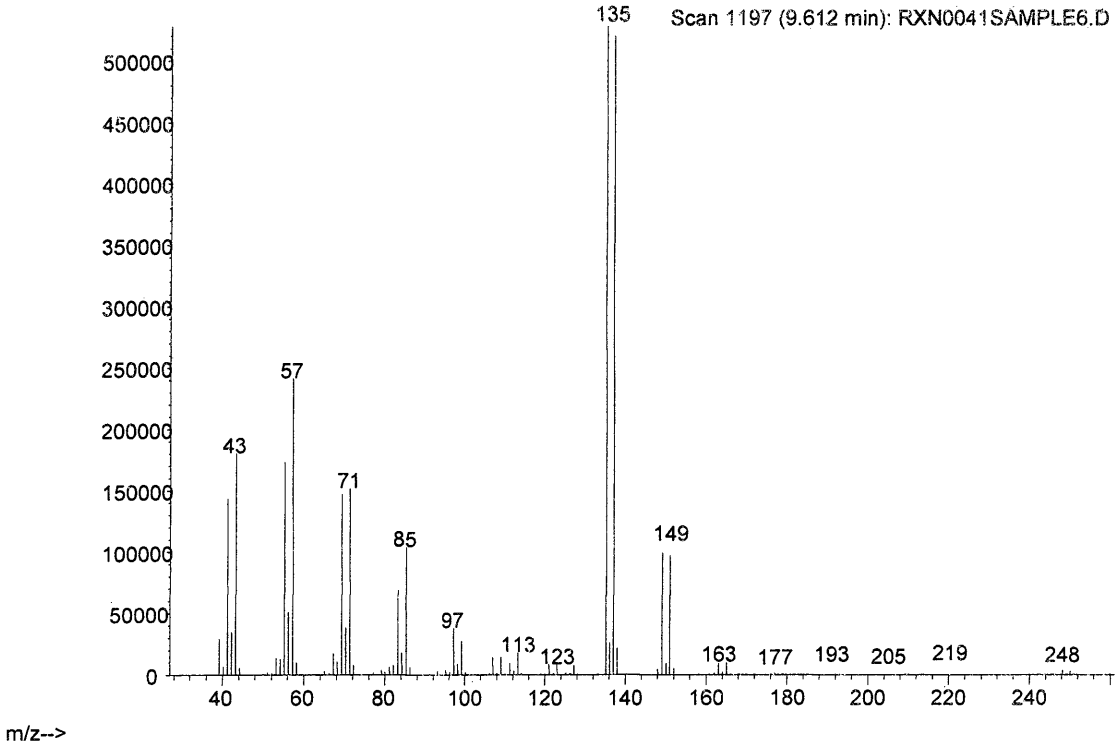




Peak	Carbon	Hz	ppm	Relative Intensity
1	C_{12}	1452.43	14.434	13.892
2	C_{11}	2313.35	22.990	16.385
3	C_3	2864.99	28.473	17.320
4	C_4-C_9	2924.97	29.069	17.488
5	C_4-C_9	2980.97	29.625	18.234
6	C_4-C_9	2992.04	29.735	20.105
7	C_4-C_9	3001.76	29.832	20.386
8[a]	C_4-C_9	3009.88	29.913	33.433
9	C_{10}	3239.93	32.199	17.495
10	C_1	3334.46	33.138	16.807
11	C_2	3456.98	34.356	15.361

[a] Integrates for 2 carbons

Figure A 537: Mass Spectrum of 1-Bromododecane



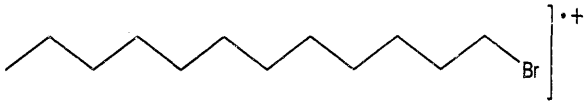
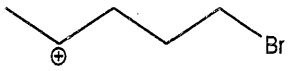
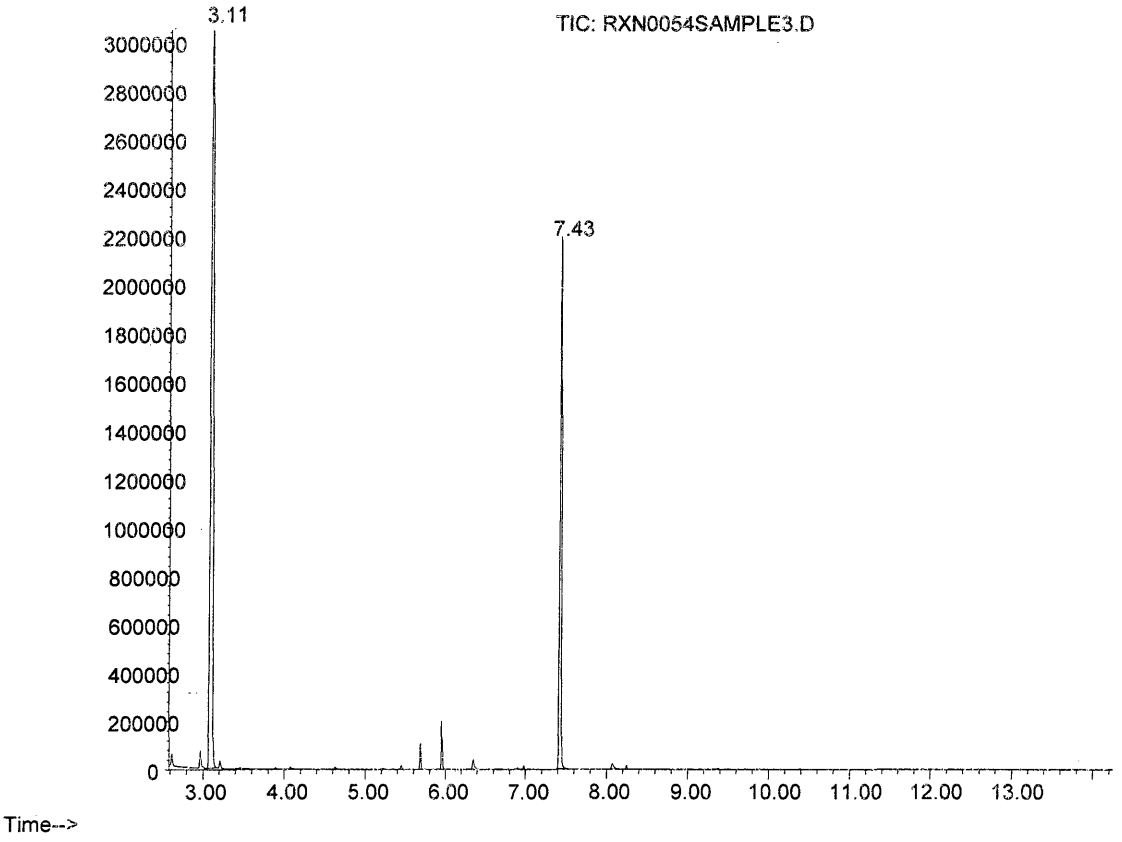
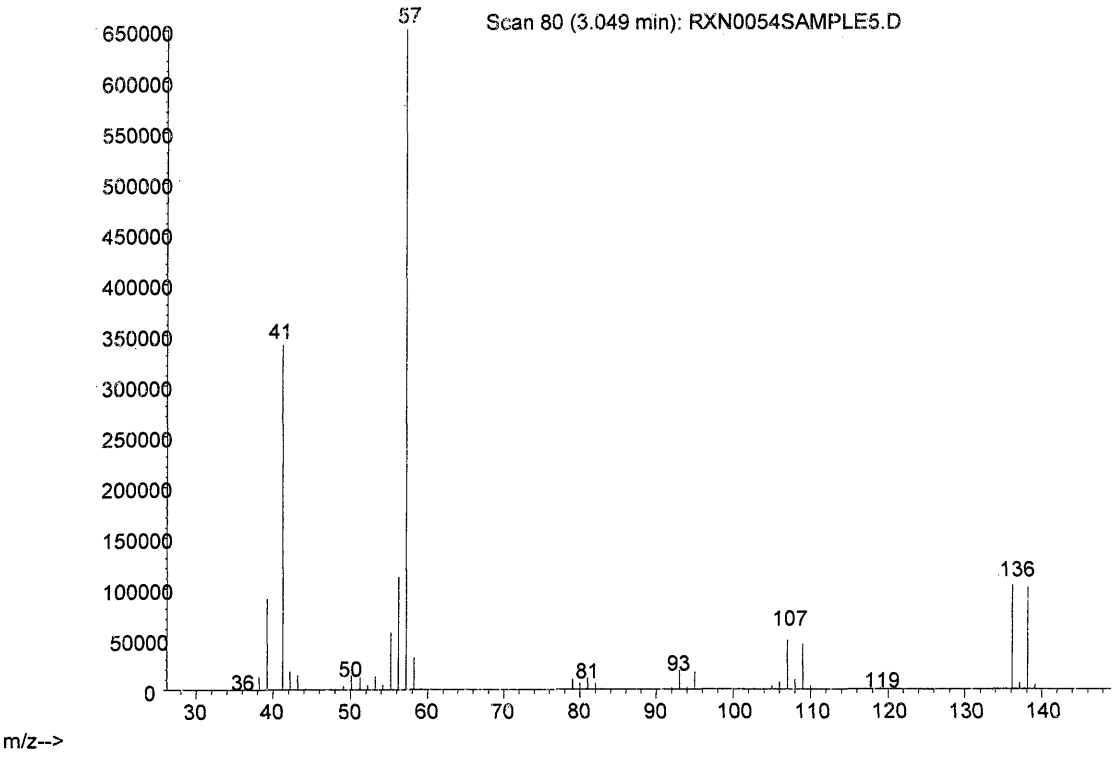
Mass	Ion / Radical	
248/250		Molecular Ion
149		
135		

Figure A 58: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate II



Retention time (min)	**Name**
3.11	1-Bromobutane
7.43	*O*-butyl-*S*-methylxanthate

Figure A 59: Mass Spectrum of 1-Bromo-butane



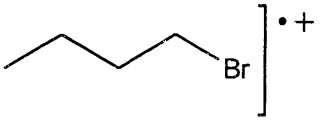
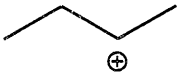
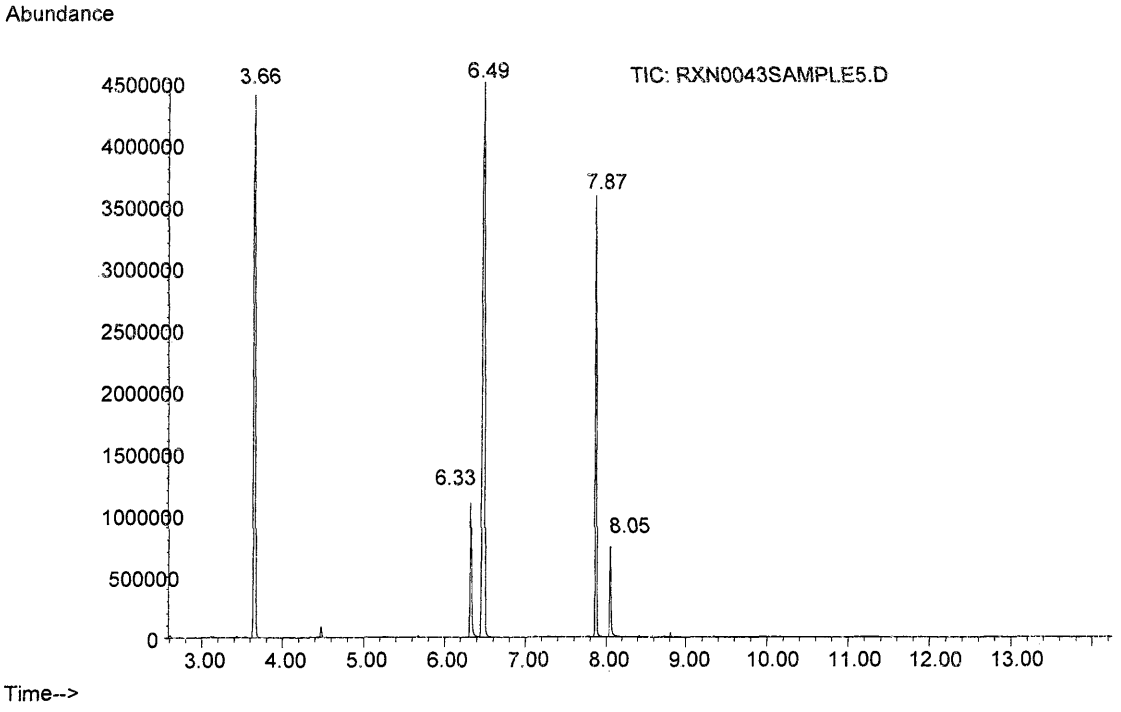
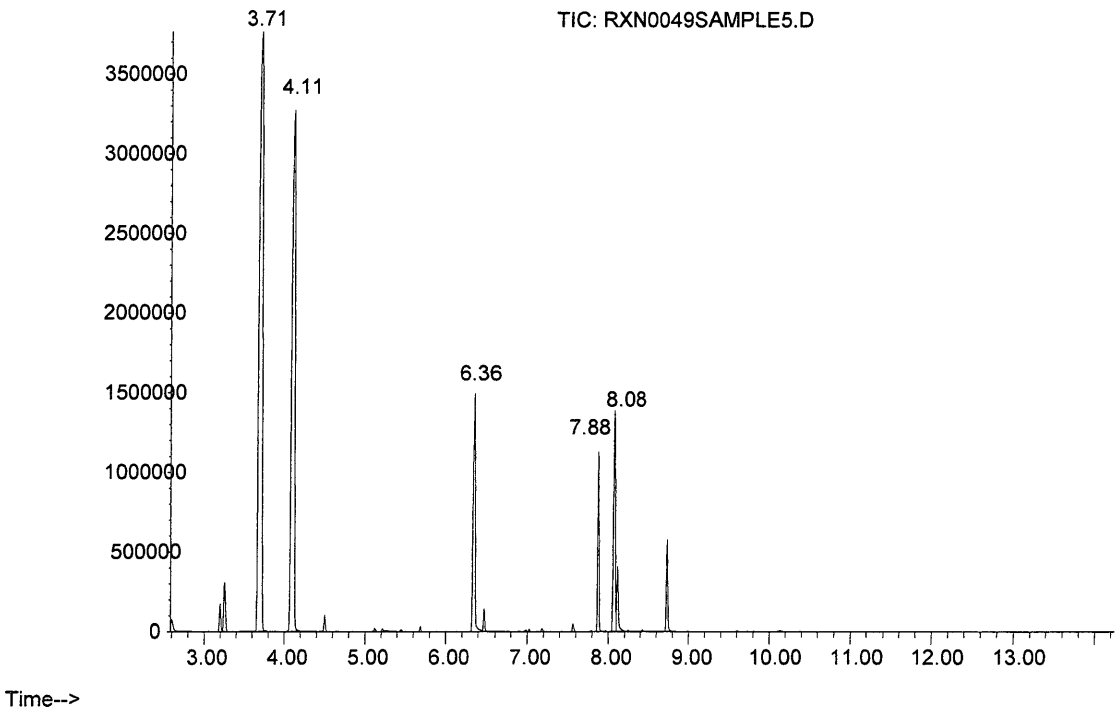
Mass	Ion / Radical	
136 / 138		Molecular Ion
57		

Figure A 60: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate III



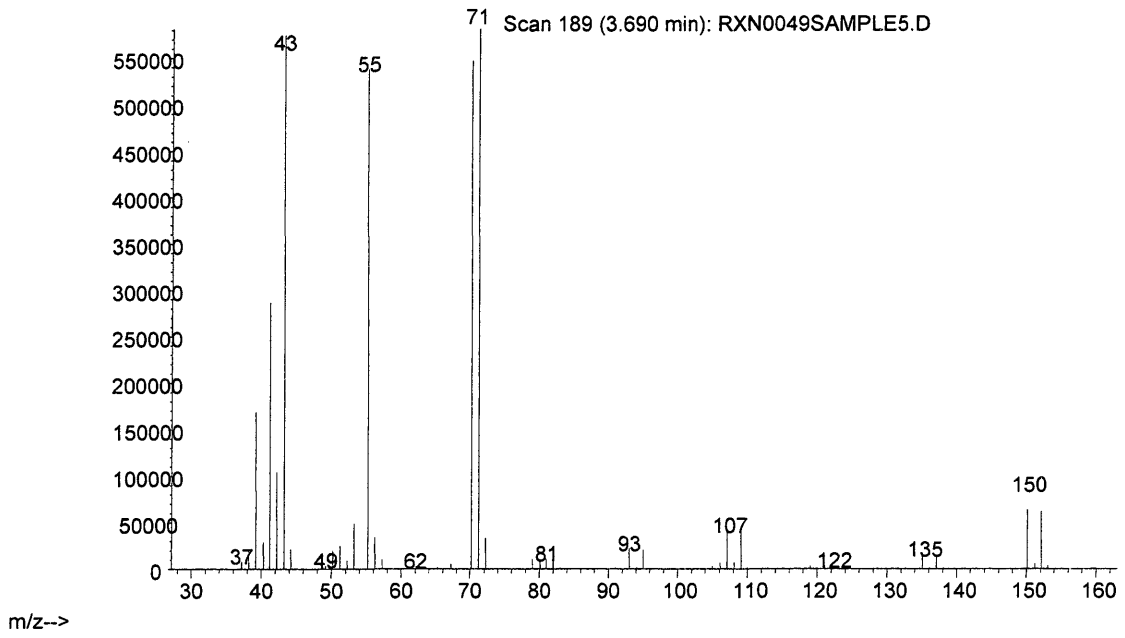
Retention time (min)	Name
3.66	1-Bromo-3-methylbutane
6.33	4-Formylmorpholine
6.49	*O*-(3-methylbutyl)-*S*-methyl-thiocarbonate
7.87	*O*-(3-methylbutyl)-*S*-methyl-xanthate
8.07	4-Thioformylmorpholine

Figure A 61: Gas Chromatograph of 2.0 Vilsmeier Equivalent Deprotection of Xanthate III



Retention time (min)	**Name**
3.71	1-Bromo-3-methylbutane
4.11	Methyl bromothiolformate
6.36	4-Formylmorpholine
7.88	*O*-(3-methylbutyl)-*S*-methylxanthate
8.08	4-Thioformylmorpholine

Figure A 62: Mass Spectrum of 1-Bromo-3-methylbutane



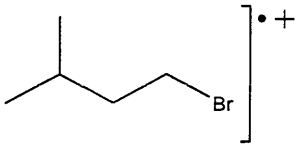
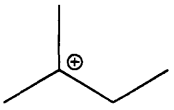
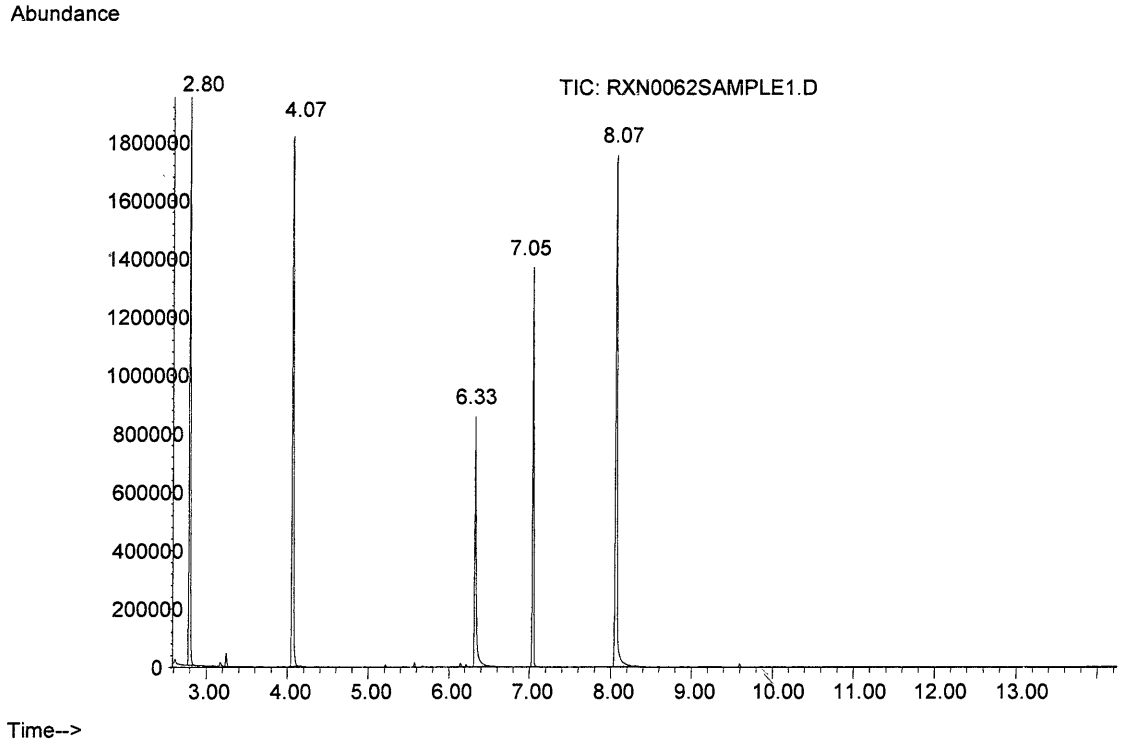
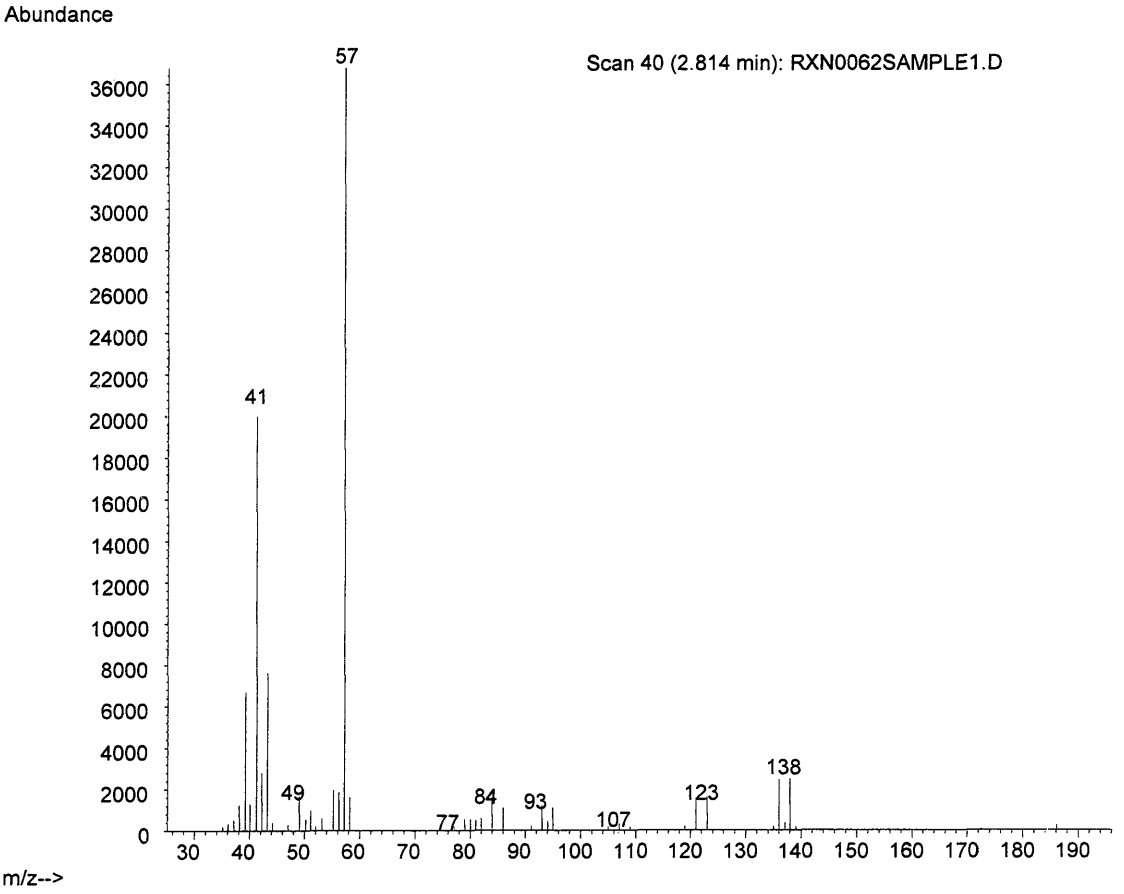
Mass	Ion / Radical	
150 / 152		Molecular Ion
71		

Figure A 63: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate IV



Retention time (min)	Name
2.80	1-Bromo-2-methylpropane
4.05	Methyl bromothiolformate
6.33	4-Formylmorpholine
7.05	*O*-(2-methylpropyl)-*S*-methylxanthate
8.07	4-Thioformylmorpholine

Figure A 64: Mass Spectrum of 1-Bromo-2-methylpropane



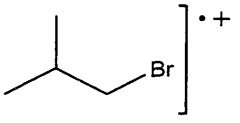
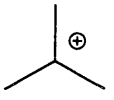
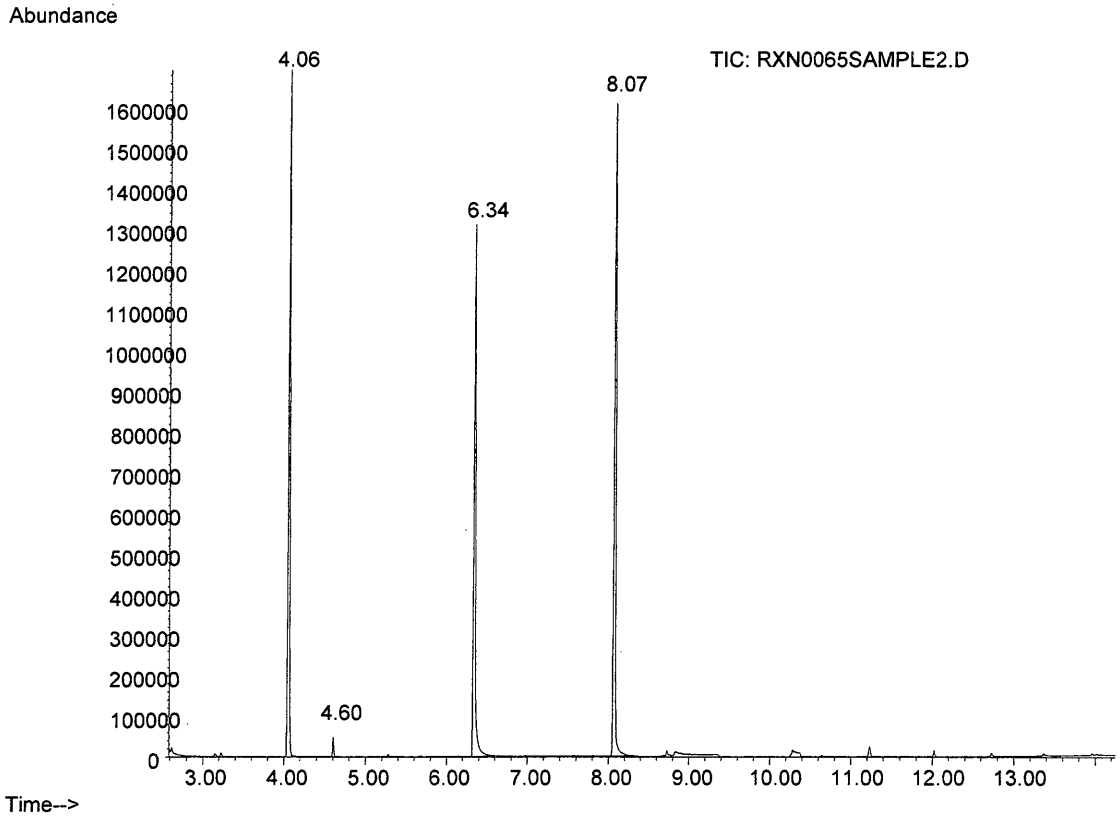
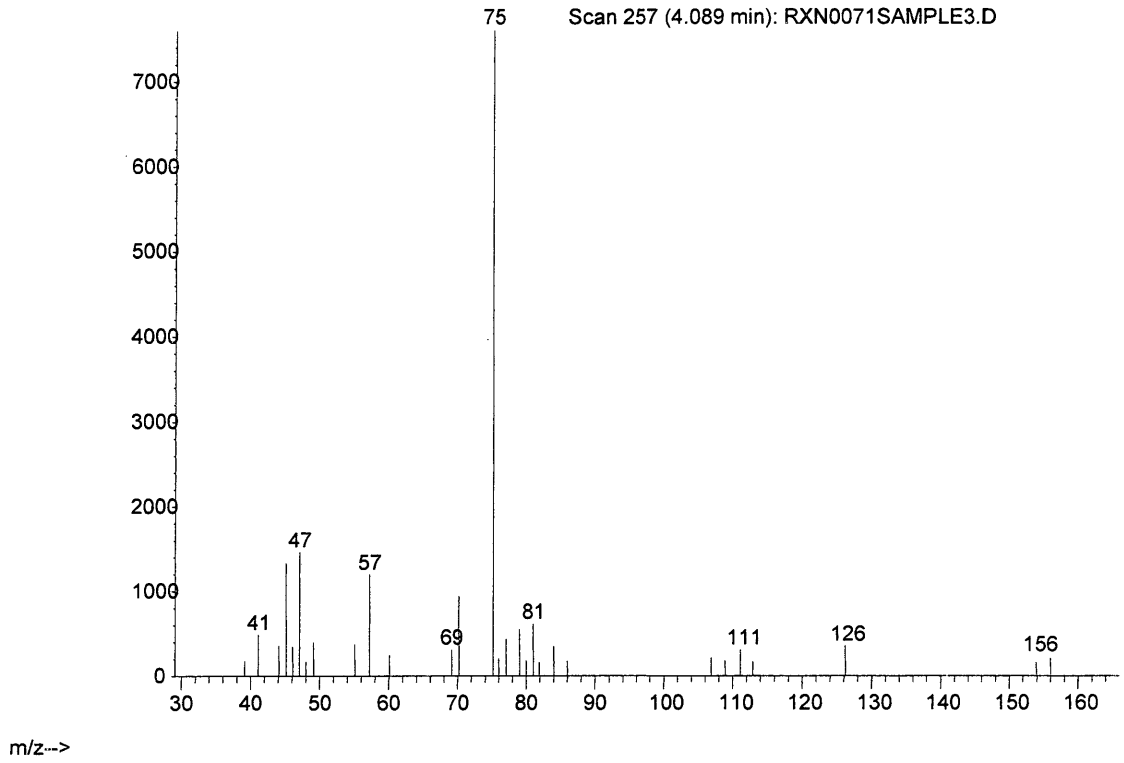
Mass	Ion / Radical	
136 / 138		Molecular Ion
57		

Figure A 65: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate V: Reaction Pot at 1 Hour



Retention time (min)	Name
4.05	Methyl bromothiolformate
4.60	*O*-(1-methylethyl)-*S*-methylthiocarbonate
6.33	4-Formylmorpholine
8.07	4-Thioformylmorpholine

Figure A 66: Mass Spectrum of Methyl bromothiolformate



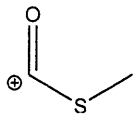
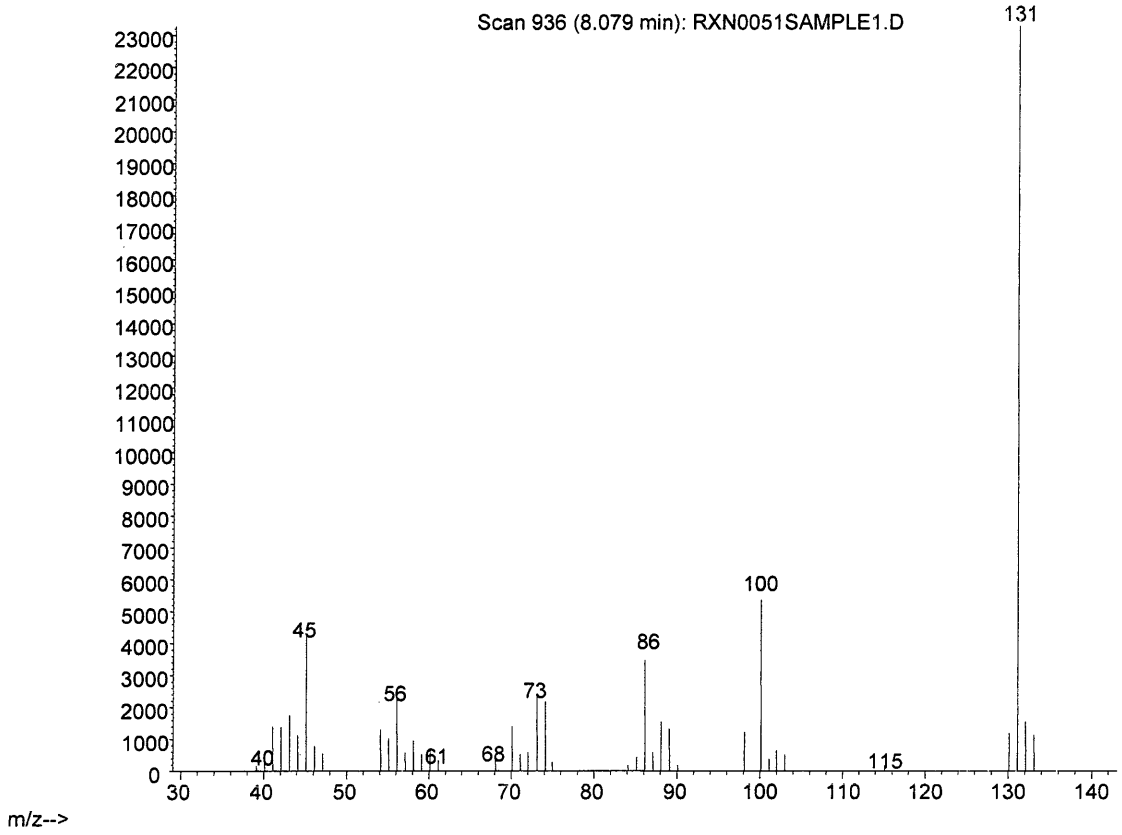
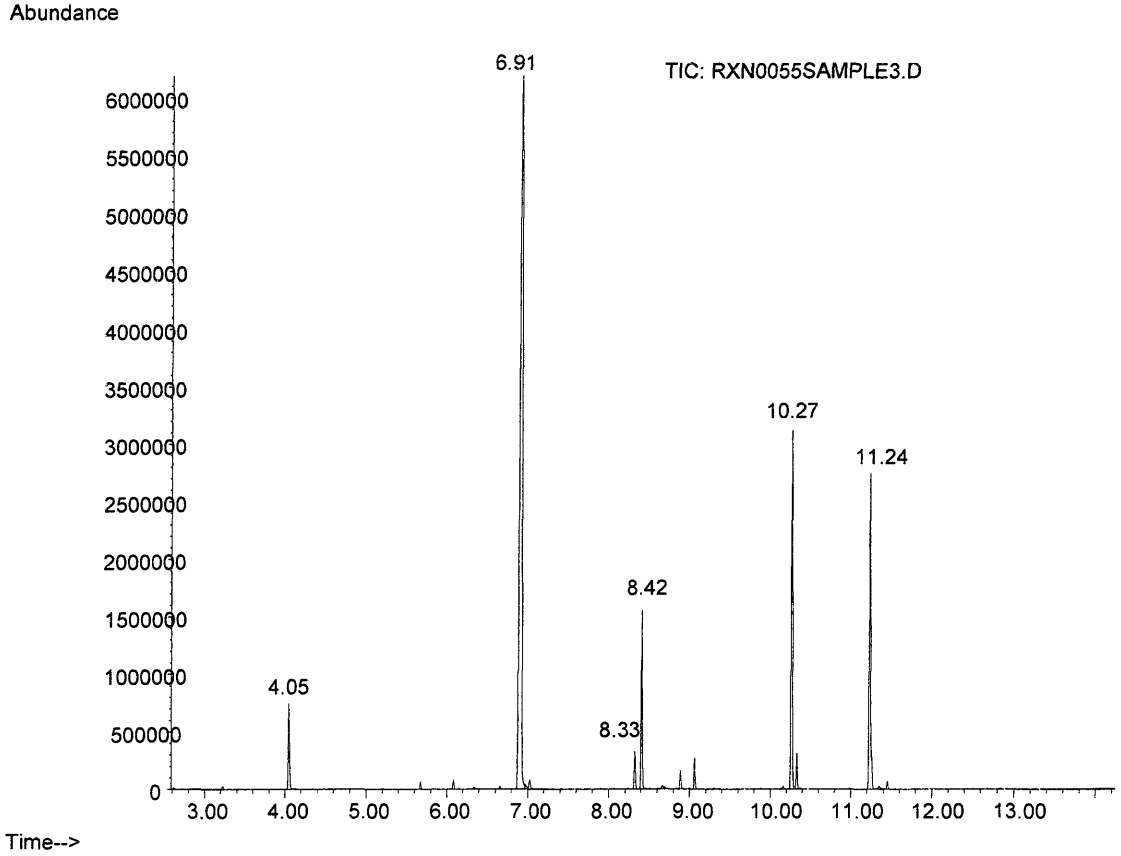
Mass	**Ion / Radical**
154 / 156	Molecular Ion
75	

Figure A 67: Mass Spectrum of 4-Thioformylmorpholine



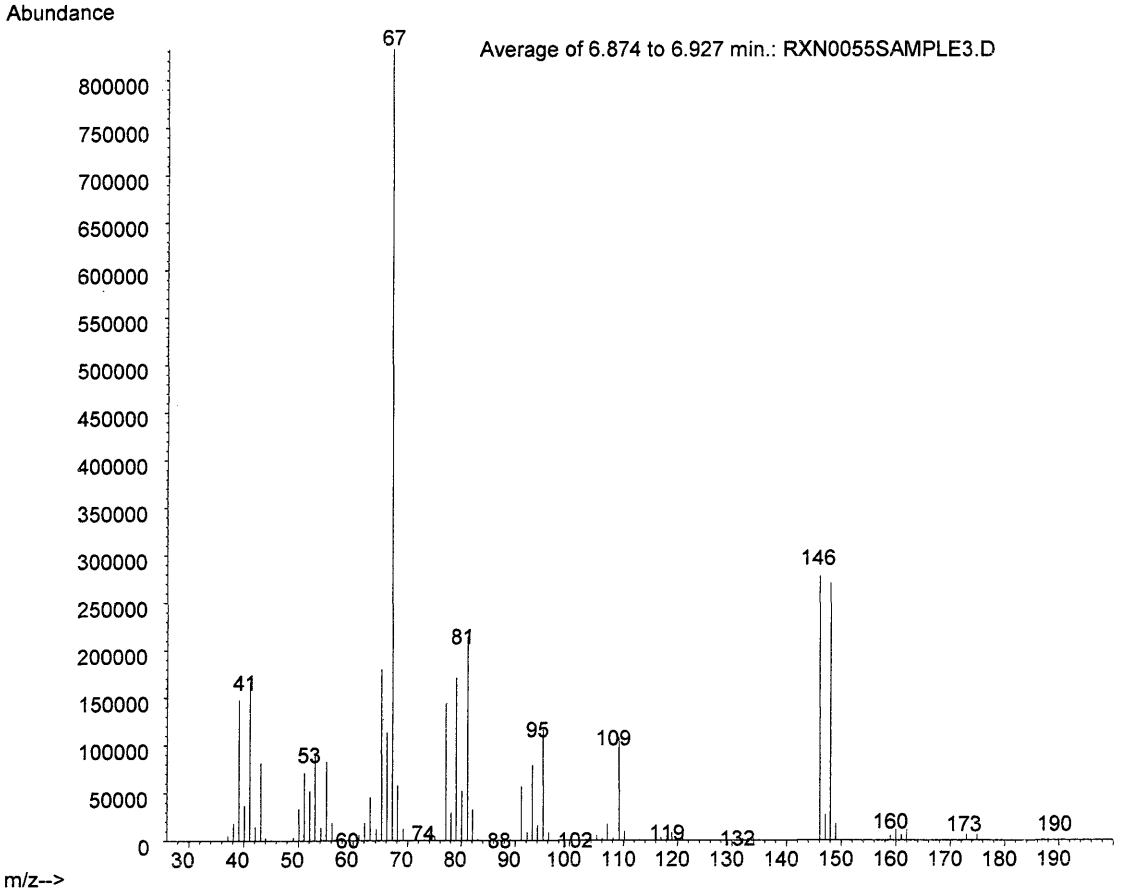
Mass	Ion / Radical
131	Molecular Ion
100	

Figure A 68: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate VI



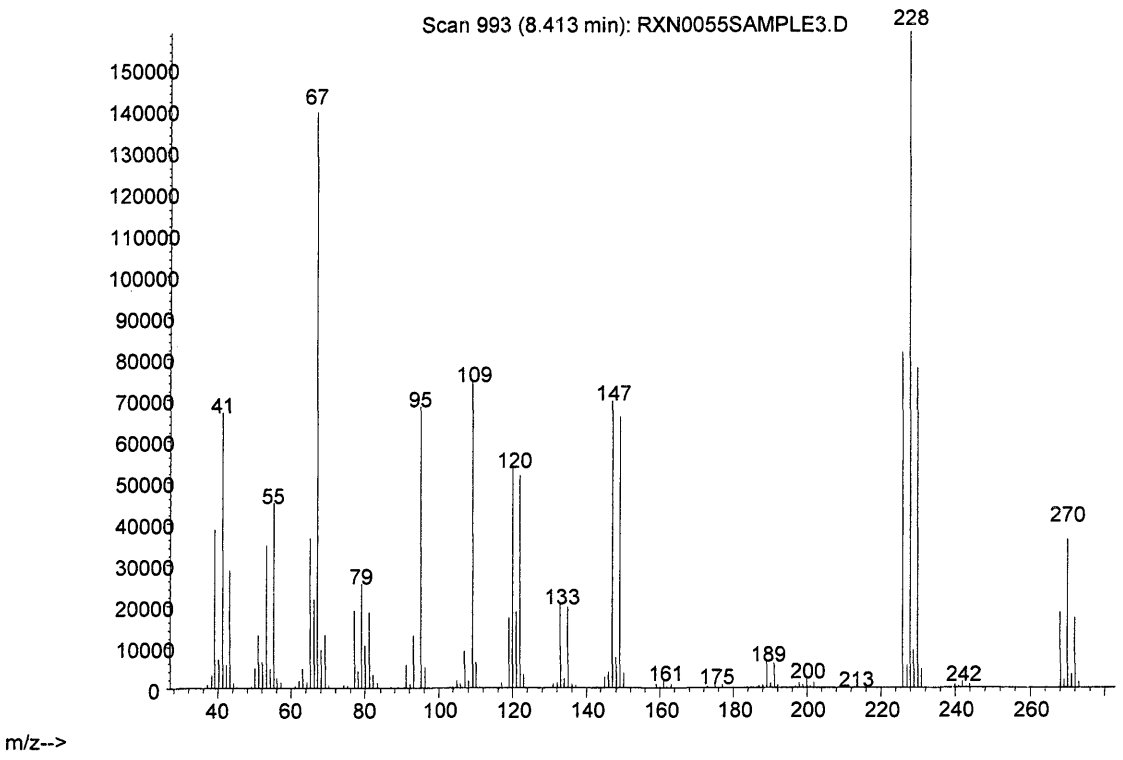
Retention time (min)	Name
4.05	Methyl bromothiolformate
6.91	1-Bromo-oct-3-yne
8.33	1,4-Dibromo-oct-3-ene
8.42	1,3-Dibromo-oct-3-ene
10.27	**VI**
11.24	Unknown Compound

Figure A 69: Mass Spectrum of 1-Bromo-oct-3-yne



Mass	Ion / Radical
188/190	Molecular Ion
146/148	
109	

Figure A 70: Mass Spectrum of 1,3-Dibromo-oct-3-ene



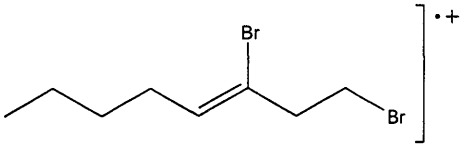
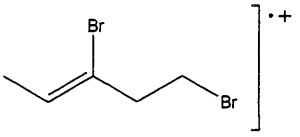
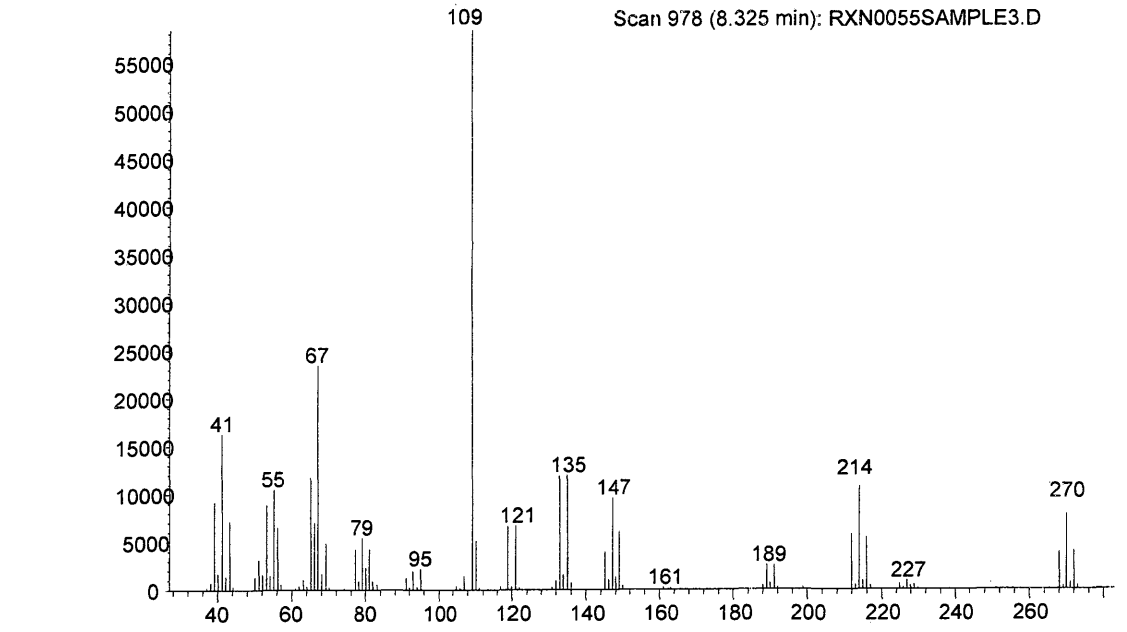
Mass	Ion / Radical	
270		Molecular Ion
228		

Figure A 71: Mass Spectrum of 1,4-Dibromo-oct-3-ene



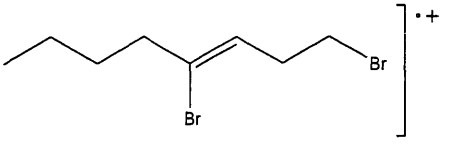
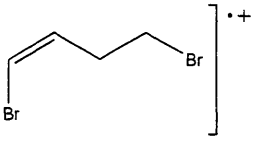
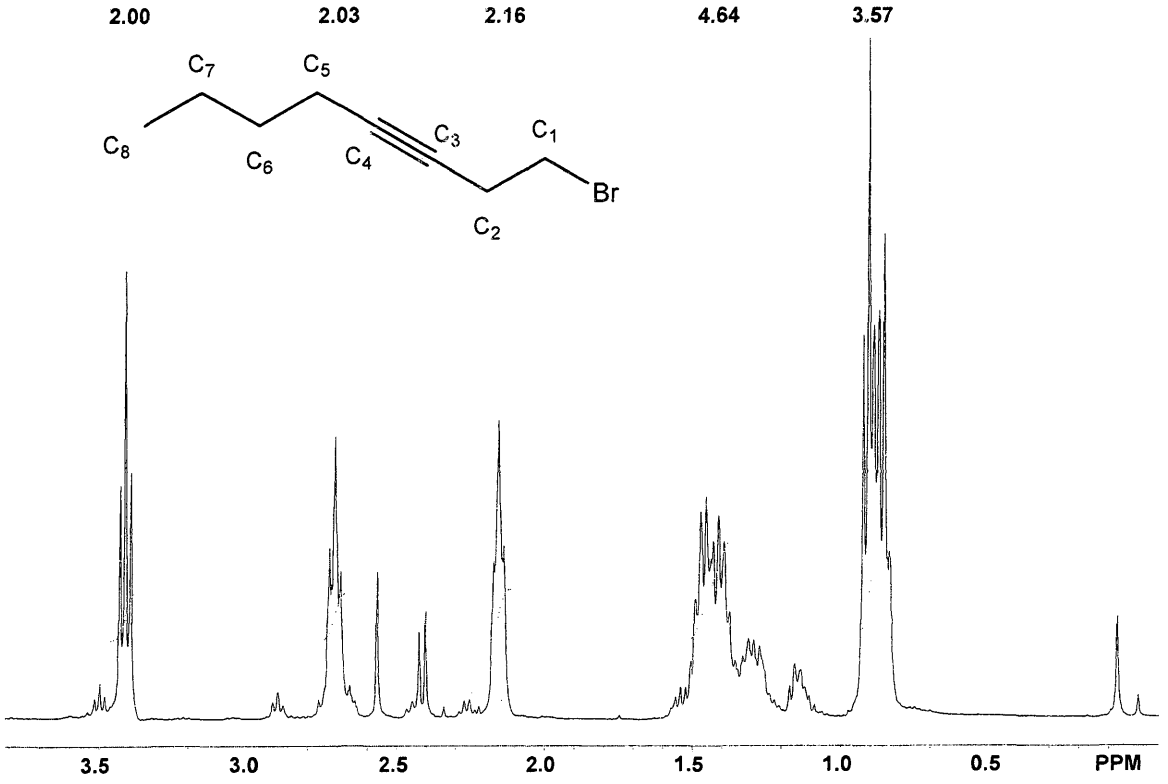
Mass	Ion / Radical	
270		Molecular Ion
214		

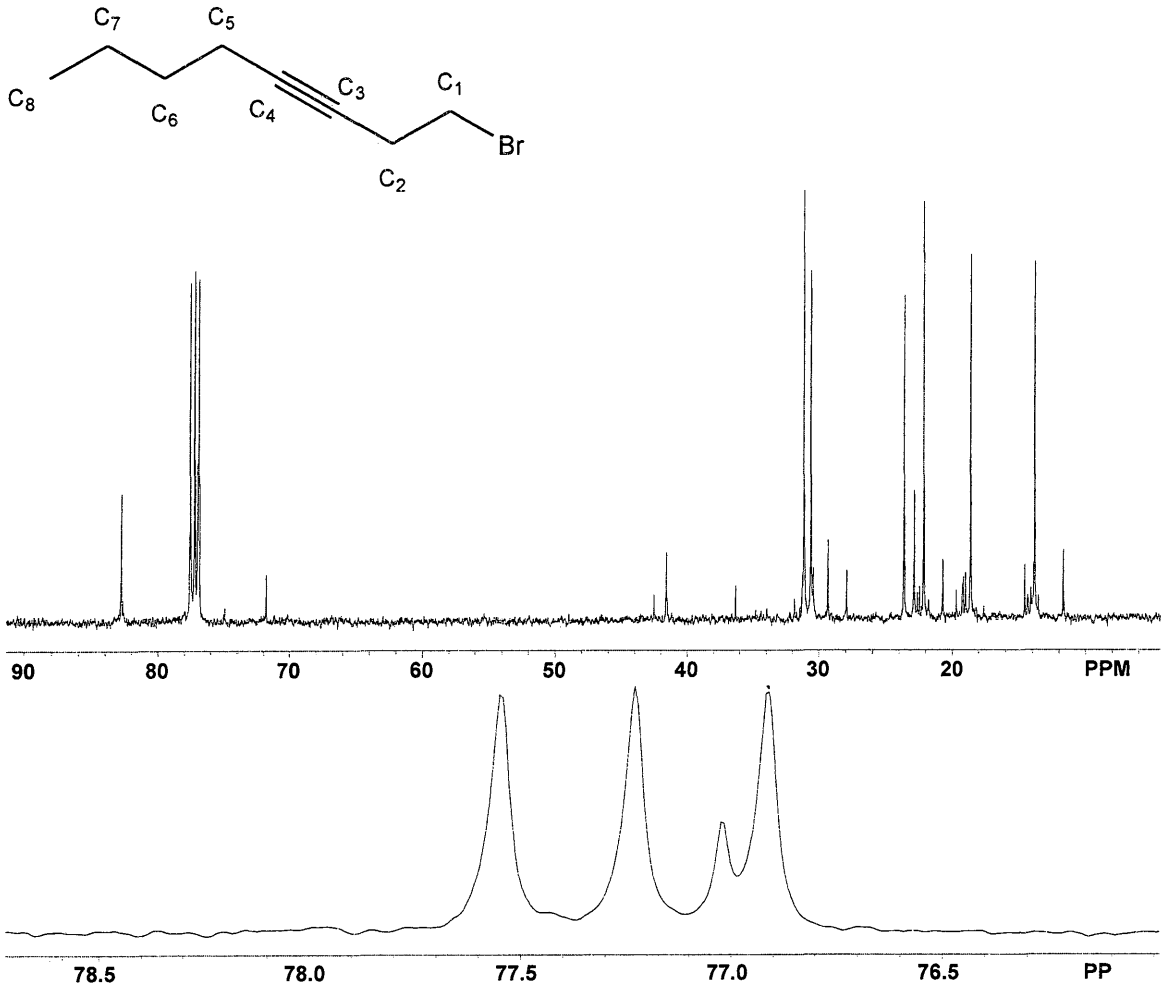
Figure A 72: ^{1}H-NMR of 1-Bromo-oct-3-yne



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_8	Triplet[a]	370.22	0.925	55.041
		362.65	**0.906**	**99.933**
		356.17	0.890	58.820
C_6,C_7	Multiplet	549.51	1.373	16.080
		557.27	1.393	26.313
		564.70	**1.411**	**29.887**
		572.00	1.430	25.986
		582.03	**1.455**	**32.391**
		588.50	1.471	29.804
		596.41	1.491	16.821
C_5	Triplet of	868.60	2.171	23.417
	Triplets	**861.83**	**2.154**	**44.561**
		855.01	2.137	25.271
C_2	Triplet of	1091.09	2.727	26.263
	Triplets	**1083.81**	**2.709**	**42.408**
		1076.55	2.691	21.195
C_1	Triplet	1371.65	3.428	35.925
		1364.18	**3.409**	**65.076**
		1357.19	3.392	35.341

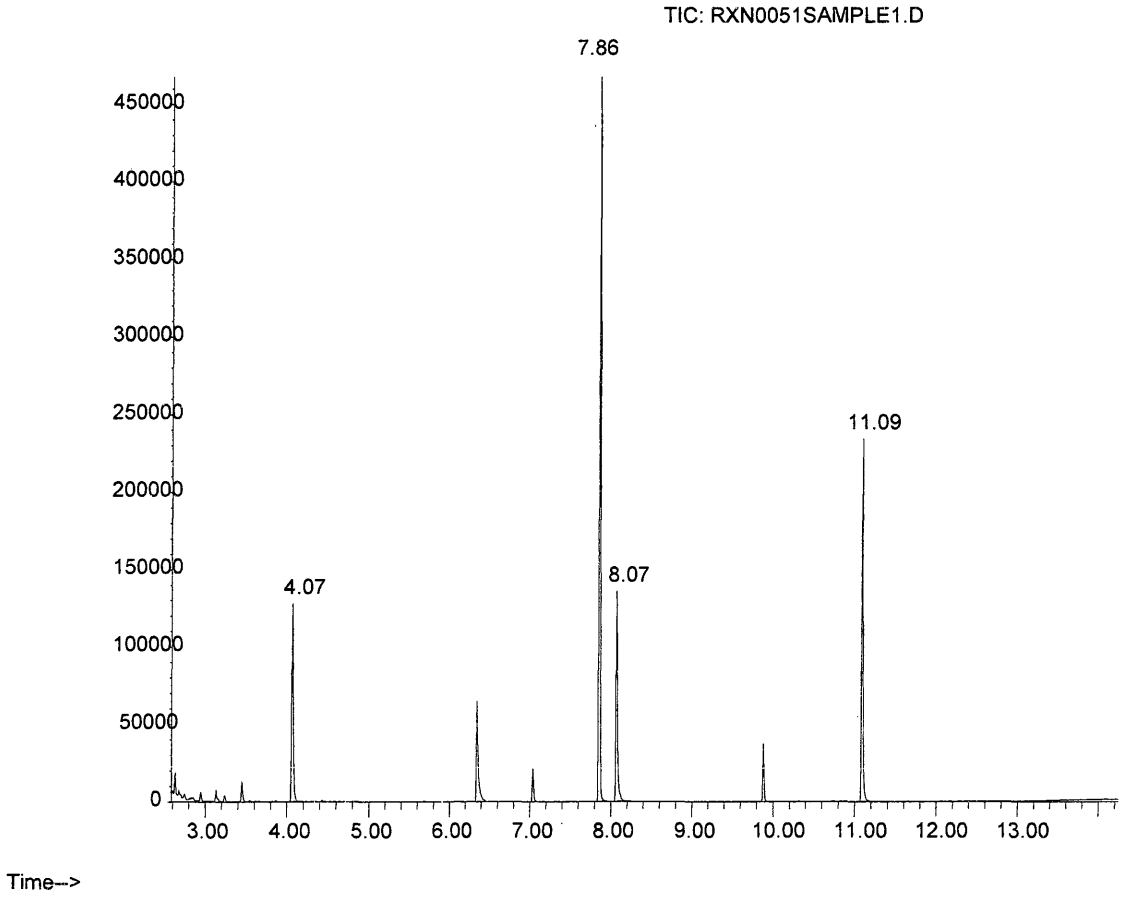
[a] The C_8-triplet is overlapped with the triplet from the unreacted VI

Figure A 73: ^{13}C-NMR of 1-Bromo-oct-3-yne



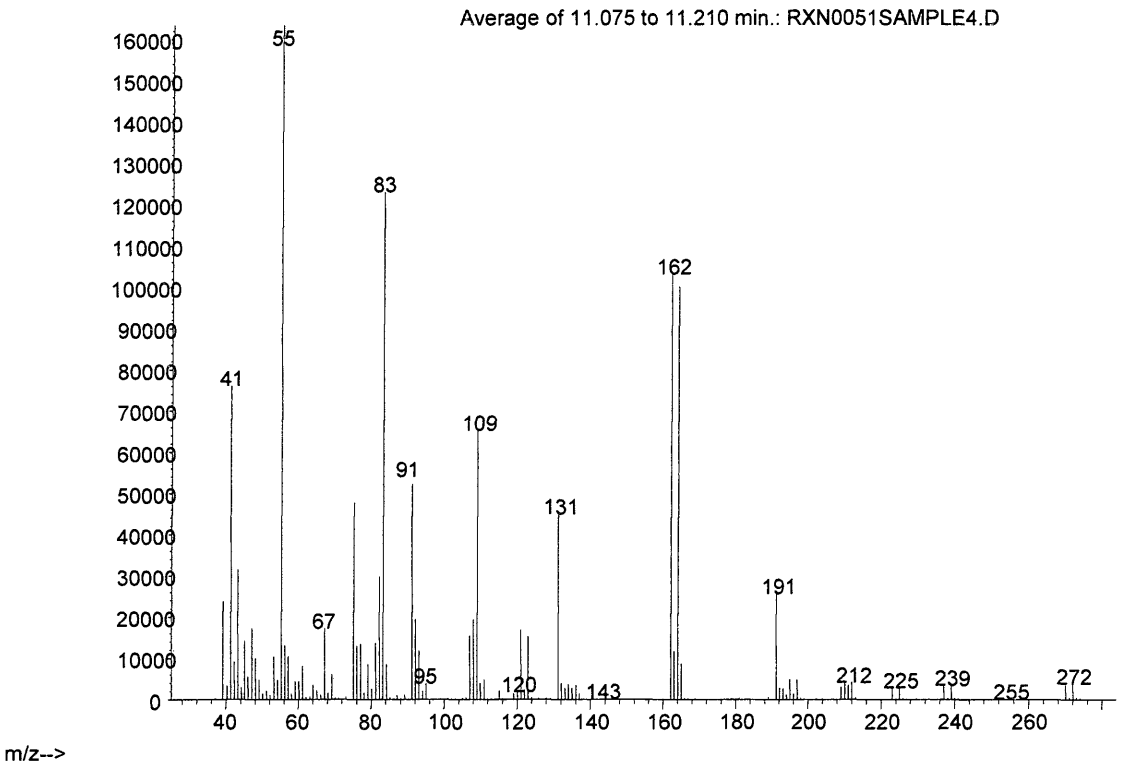
Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1396.29	13.876	84.746
2	C_5	1875.02	18.634	83.769
3	C_2	2229.91	22.161	99.039
4	C_7	2377.48	23.628	76.330
5	C_6	3080.60	30.615	82.002
6	C_1	3134.03	31.146	99.986
7	C_4	7749.66	77.017	35.362
8	C_3	8330.17	82.786	29.529

Figure A 74: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate VII



Retention time (min)	Name
4.07	Methyl bromothiolformate
7.86	1,6-Dimbromohexane
8.07	4-Thioformylmorpholine
11.09	*O*-(6-bromohexyl)-*S*-methylxanthate

Figure A 75: Mass Spectrum of *O*-(6-bromohexyl)-*S*-methylxanthate



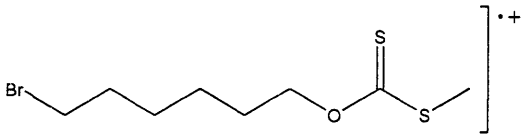
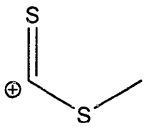
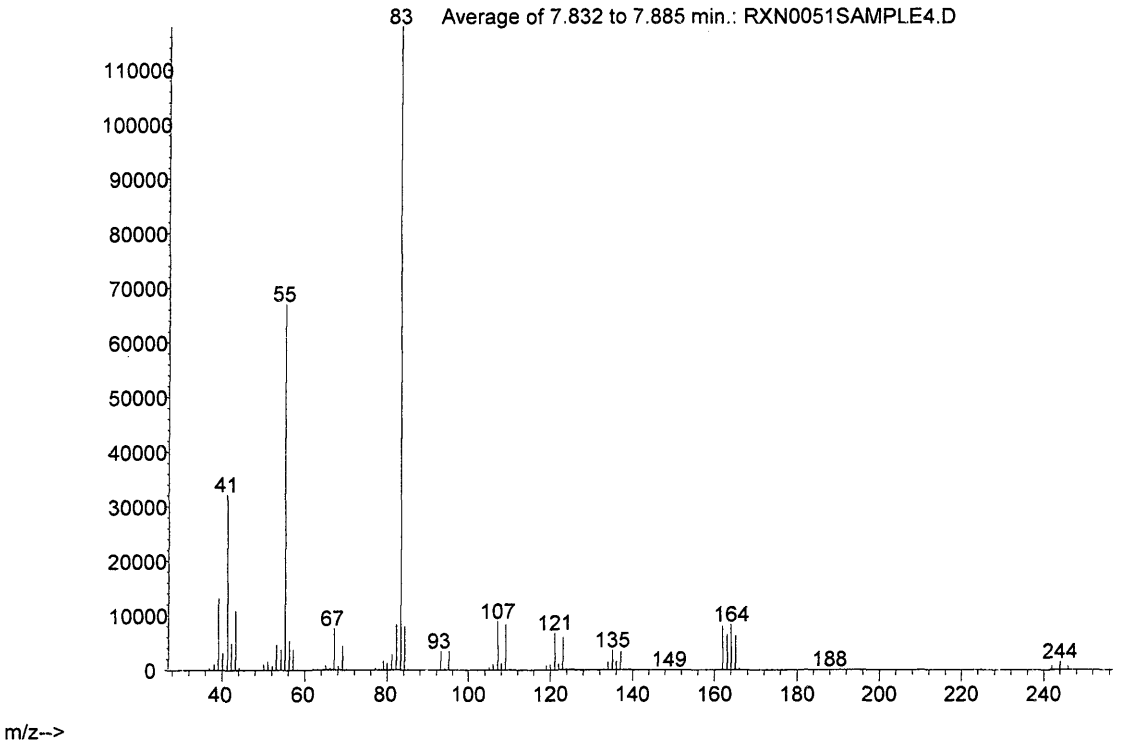
Mass	Ion / Radical	
272		Molecular Ion
91		

Figure A 76: Mass Spectrum of 1,6-Dibromohexane



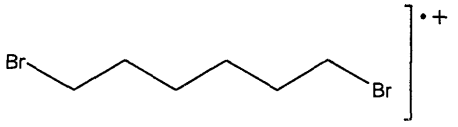
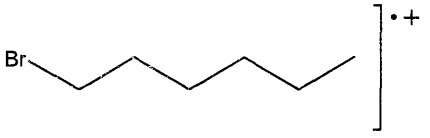
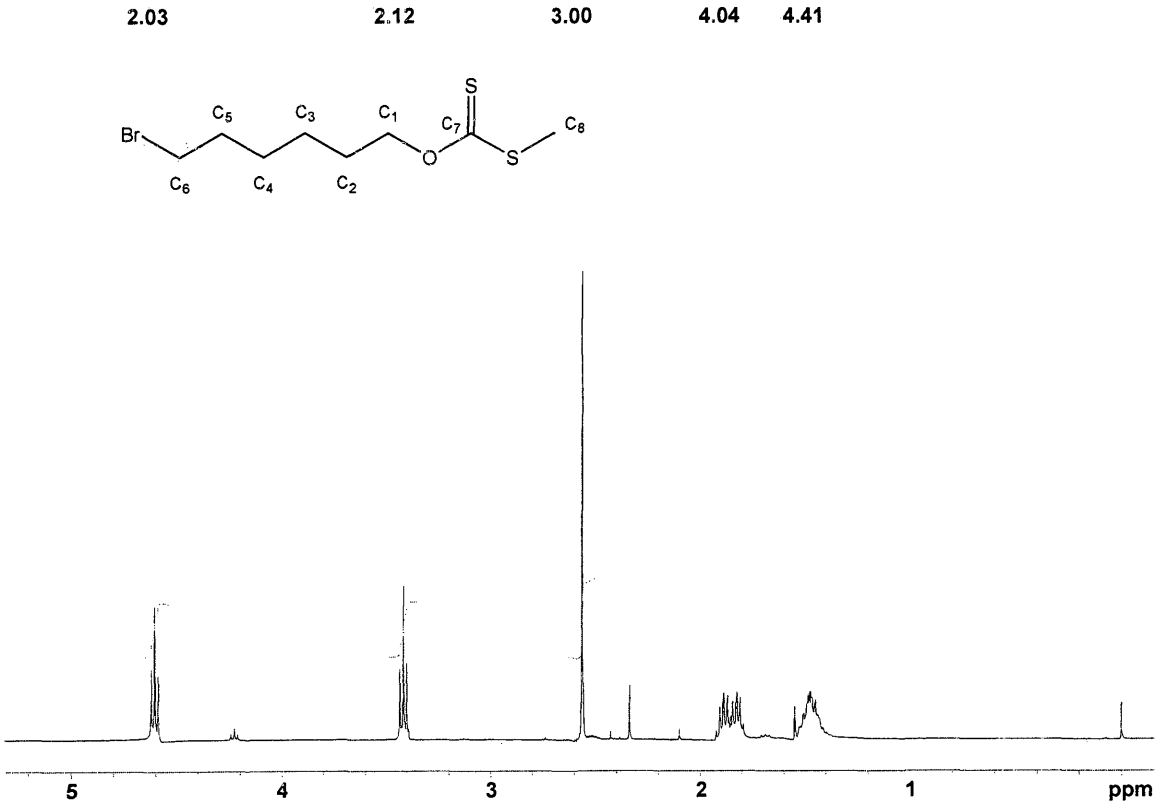
Mass	Ion / Radical	
244		Molecular Ion
164		

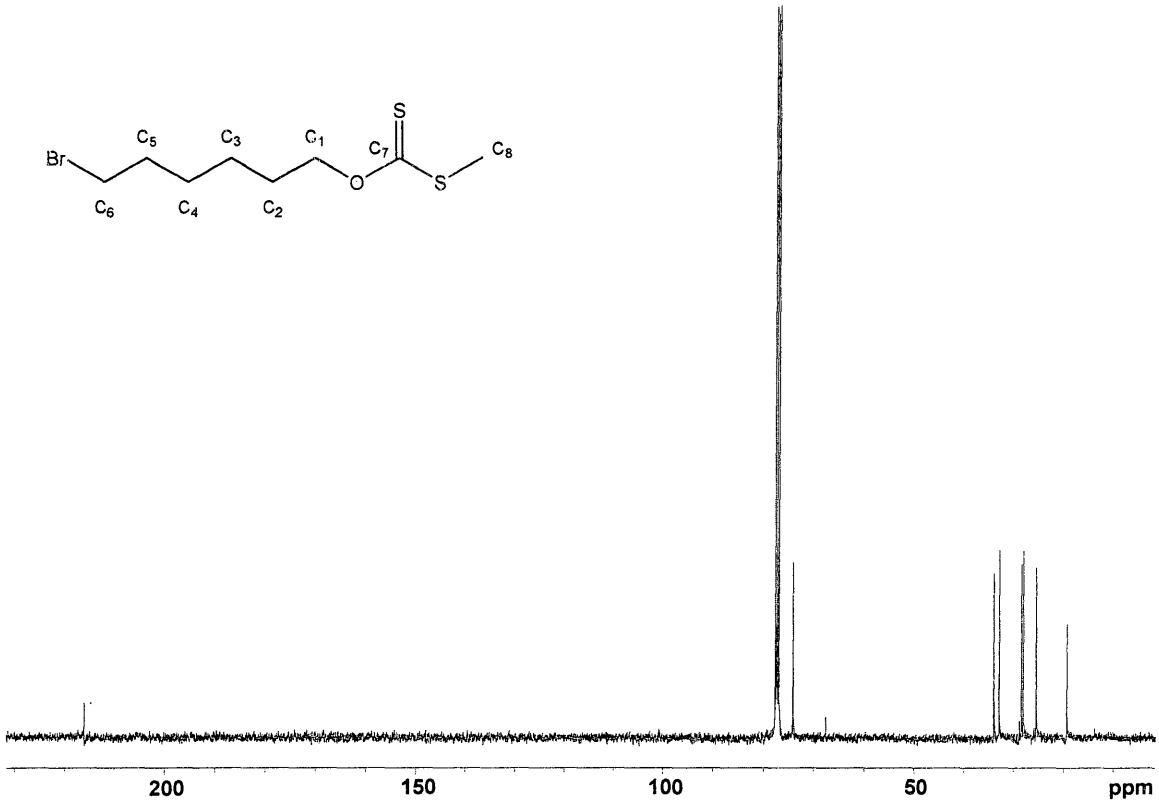
Figure A 77: ^{1}H-NMR of *O*-(6-bromohexyl)-*S*-methylxanthate



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_3,C_4	Multiplet[a]	**591.63**	**1.479**	**10.286**
C_2,C_5	Multiplet[b]	716.51	1.791	3.282
		723.23	1.808	9.152
		730.29	**1.825**	**10.097**
		738.02	1.844	8.142
		740.90	1.852	5.092
		744.80	1.861	4.687
		747.80	1.869	9.480
		755.29	**1.888**	**9.953**
		762.27	1.905	6.986
		769.01	1.922	1.915
C_8	Singlet	**1025.66**	**2.563**	**104.726**
C_6	Triplet	1361.07	3.402	17.799
		1367.87	**3.419**	**33.901**
		1374.28	3.435	16.129
C_1	Triplet	1835.74	4.588	14.208
		1842.01	**4.604**	**30.203**
		1848.81	4.621	16.068

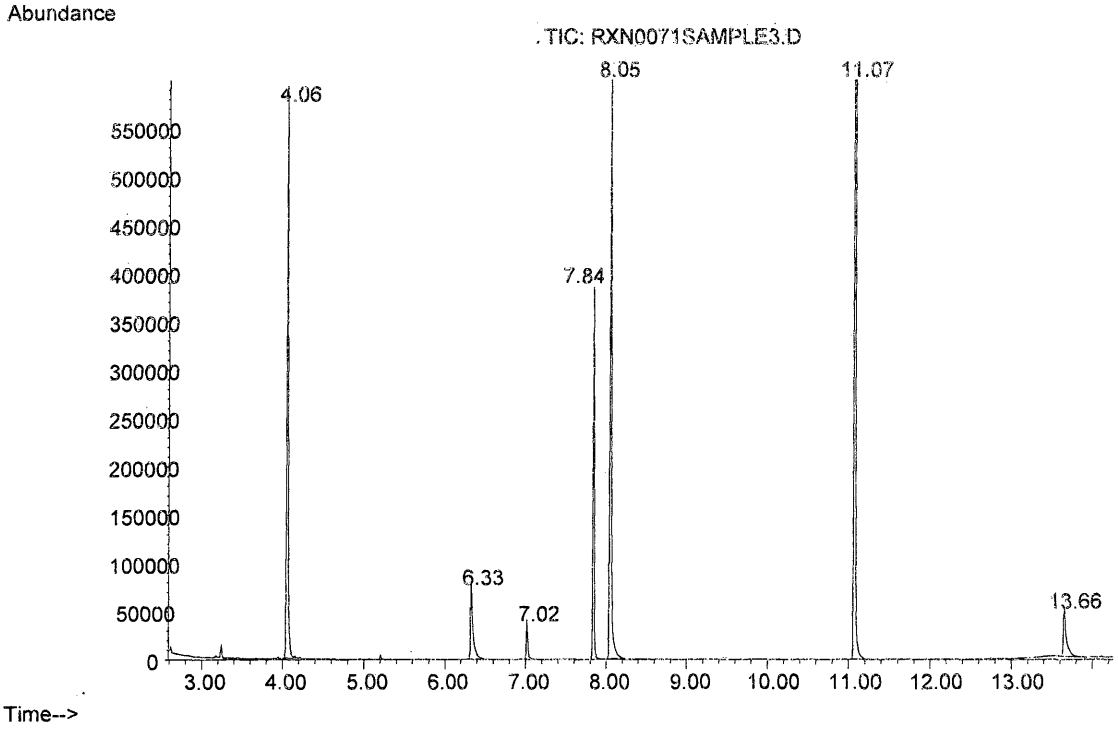
[a]Overlapping multiplets of C_3 and C_4, [b]Overlapping multiplets of C_2 and C_5

Figure A 78: ^{13}C-NMR of *O*-(6-bromohexyl)-*S*-methylxanthate



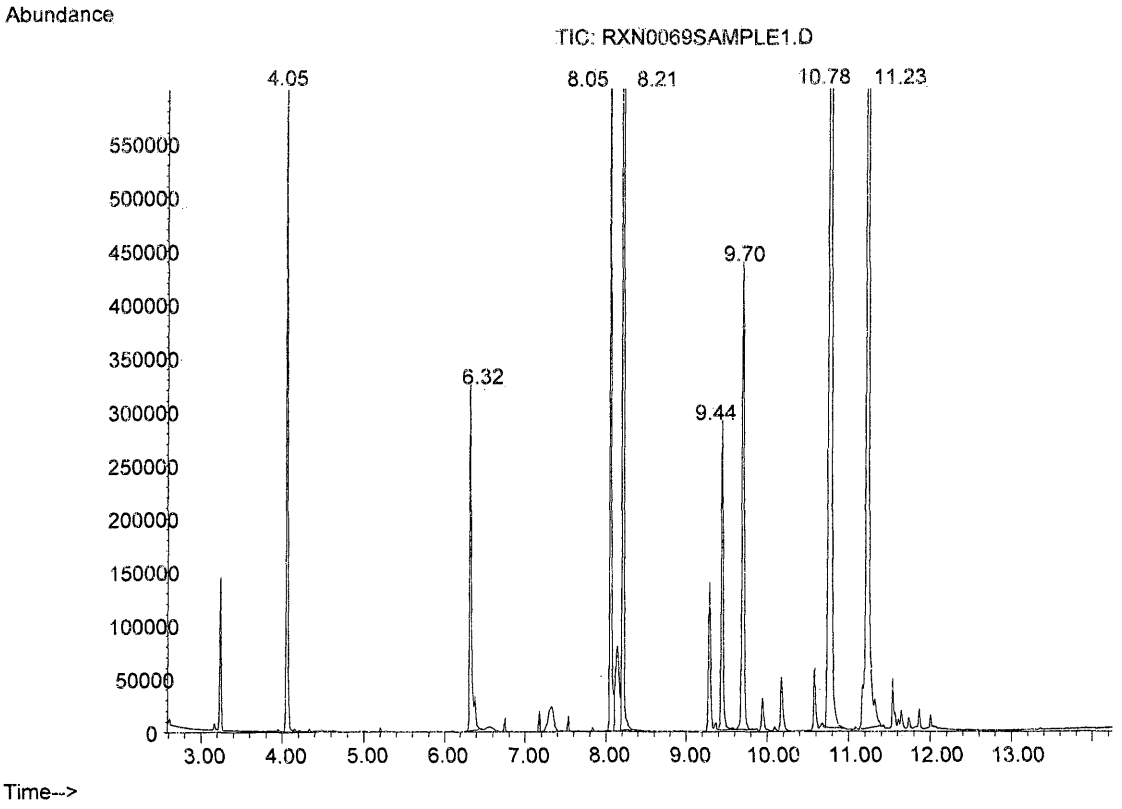
Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1943.17	19.311	15.965
2	C_3	2563.92	25.480	23.257
3	C_4	2827.17	28.097	25.181
4	C_2	2860.53	28.428	24.467
5	C_6	3308.81	32.883	26.718
6	C_5	3417.06	33.959	23.288
7	C_1	7459.14	74.130	24.213
8	C_7	21742.61	216.080	4.751

Figure A 79: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate VIII



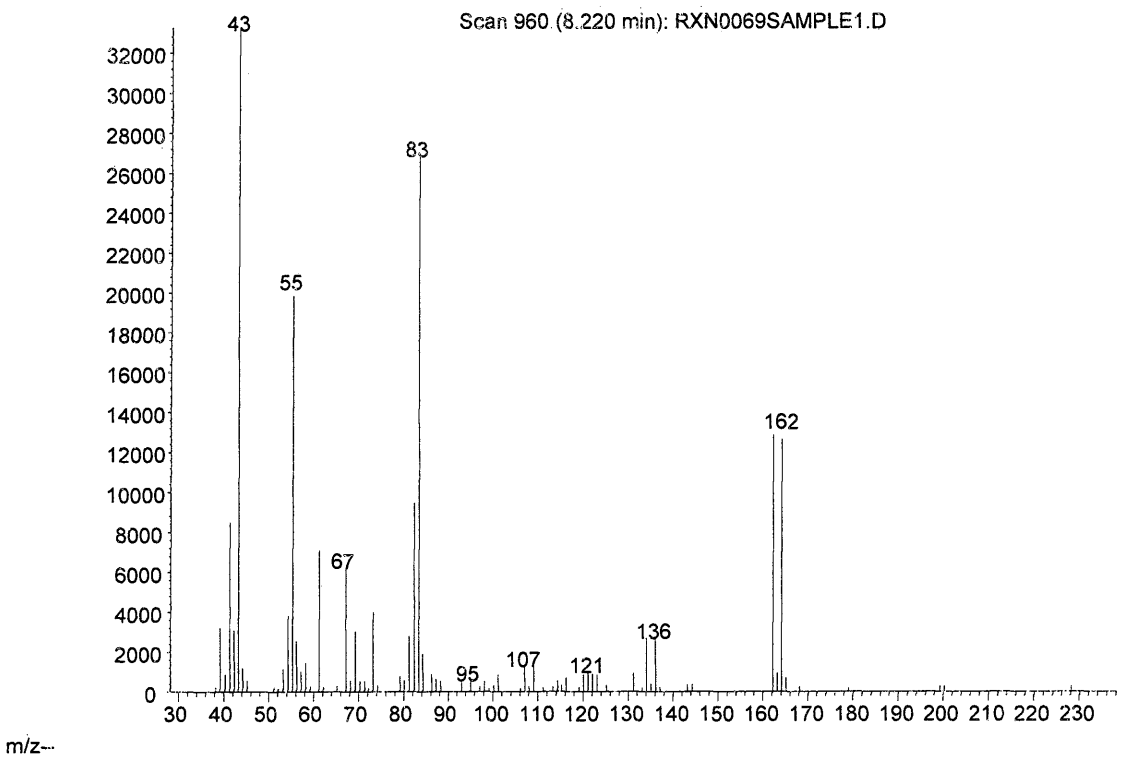
Retention time (min)	**Name**
4.06	Methyl bromothiolformate
6.33	4-Formylmorpholine
7.02	Dimethyl trithiocarbonate
7.84	1,6-Dimbromohexane
8.05	4-Thioformylmorpholine
11.07	*O*-(6-bromohexyl)-*S*-methylxanthate
13.66	**VIII**

Figure A 80: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate IX



Retention time (min)	Name
4.05	Methyl bromothiolformate
6.32	4-Formylmorpholine
8.05	4-Thioformylmorpholine
8.21	6-Bromohexyl acetate
9.44	Unknown
9.70	Unknown
10.78	**IX**
11.23	Unknown

Figure A 81: Mass Spectrum of 6-Bromohexyl acetate



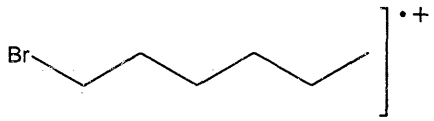
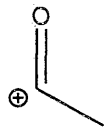
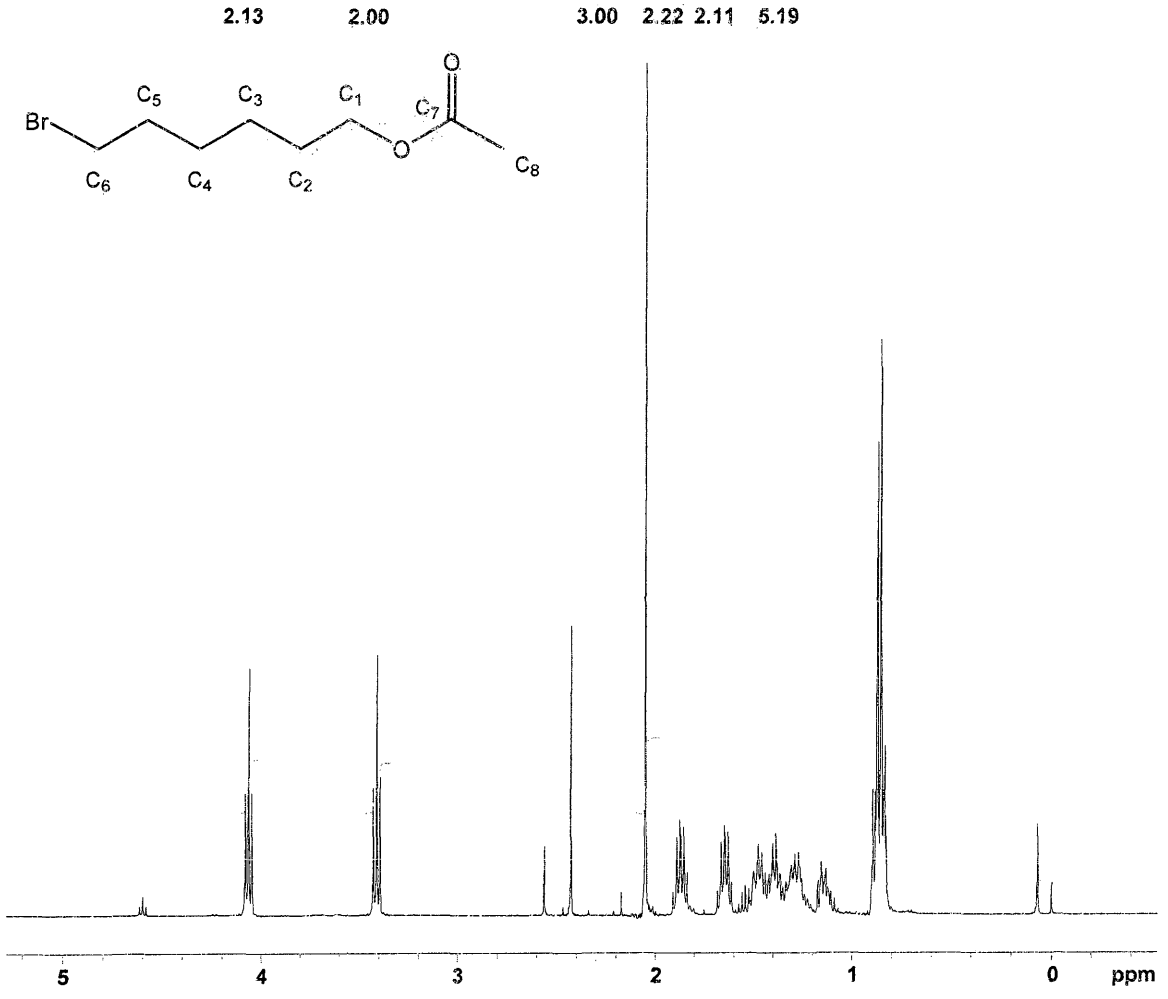
Mass	Ion / Radical
162/164	
43	

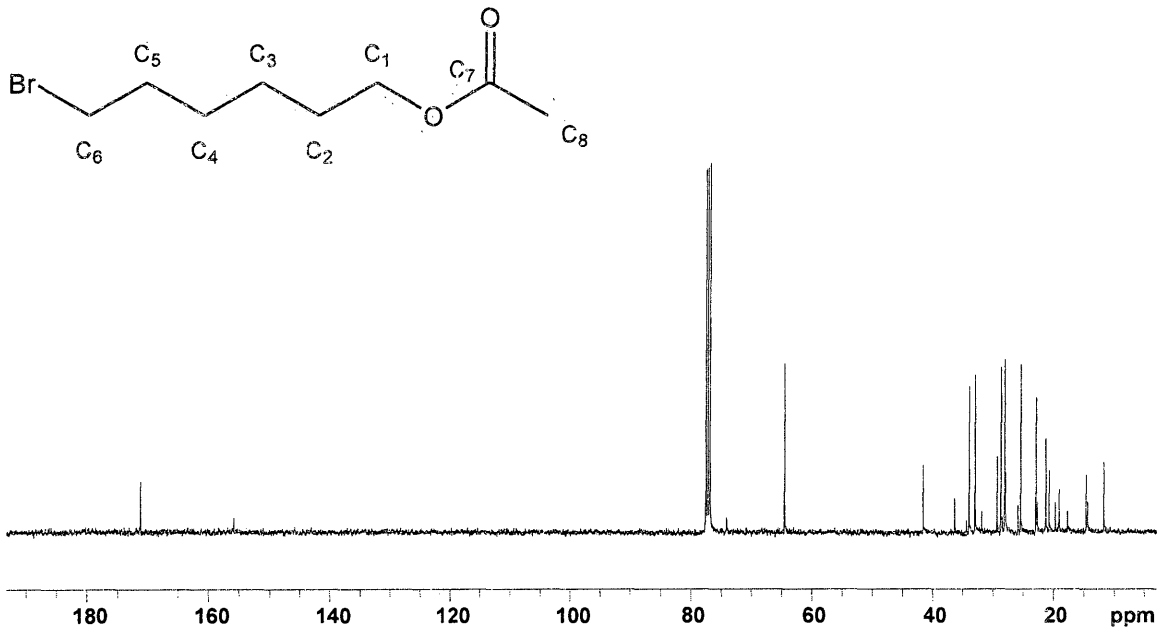
Figure A 82: ^{1}H-NMR of 6-Bromohexyl acetate



Parent Carbon	Splitting	Hz	ppm	Relative Intensity
C_3,C_4	Multiplet	547.30	1.368	4.888
		554.43	**1.386**	**9.856**
		561.60	1.404	8.408
		583.60	1.459	7.316
		591.02	**1.477**	**8.315**
		599.72	1.499	5.157
C_2	Pentet	645.24	1.613	3.885
		651.75	1.629	10.030
		659.05	1.647	10.601
		666.75	1.666	8.599
		673.09	1.682	2.821
C_5	Pentet	735.51	1.838	5.060
		741.90	1.854	10.594
		749.90	1.874	11.367
		756.94	1.892	9.372
		763.41	1.908	2.745
C_8	Singlet	820.43	2.050	104.179
C_8[a]	Singlet	1024.86	2.561	8.747
C_6	Triplet	1358.79	3.396	16.788
		1365.18	3.412	32.082
		1372.28	3.430	15.965
C_1	Triplet	1619.54	4.048	14.656
		1626.21	4.064	30.129
		1632.88	4.081	14.953

[a]Singlet of Impurity O-(6-acetoxy-hexyl)-s-methyl-xanthate

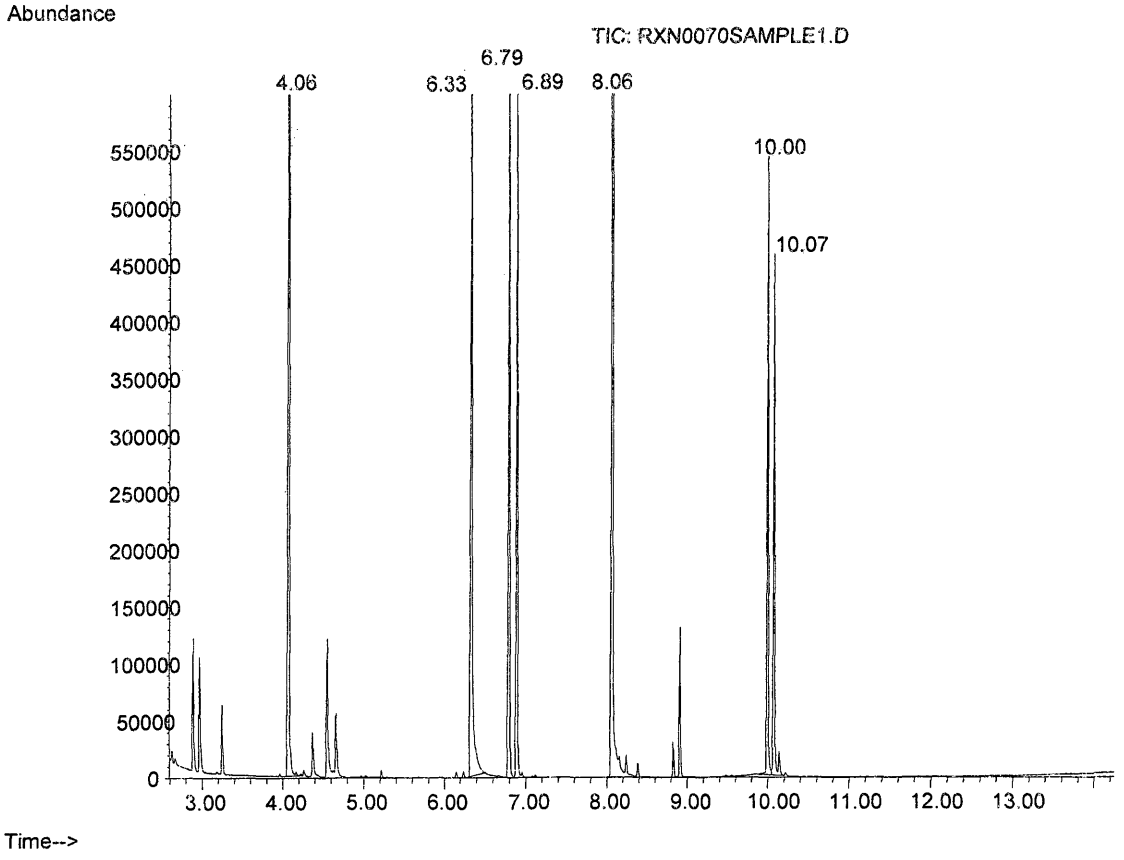
Figure A 83: ^{13}C-NMR of 6-Bromohexyl acetate



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	2302.88	22.886	37.820
2	C_3	2558.34	25.425	47.329
3	C_4	2822.60	28.051	48.300
4	C_2	2887.49	28.696	44.911
5	C_6	3306.81	32.863	44.159
6	C_5	3415.65	33.945	40.371
7	C_1	6494.69	64.545	46.750
8[a]	C_7	17230.51	171.239	13.770

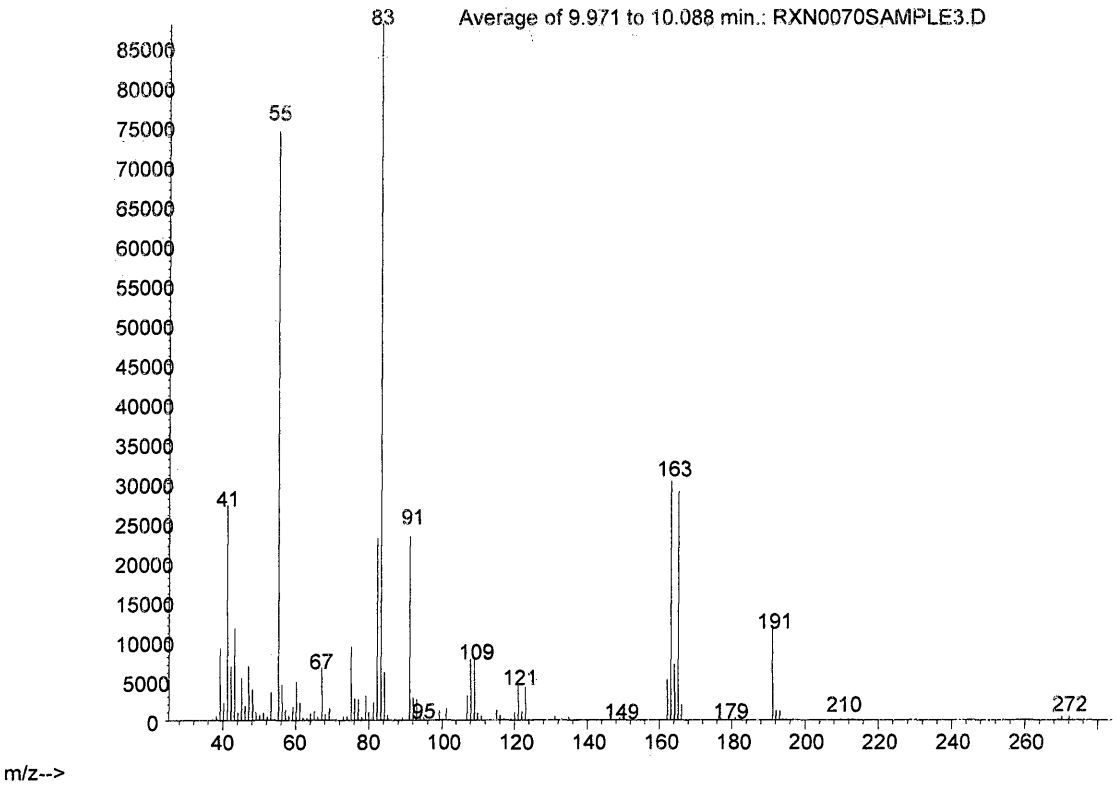
[a]Peak 8 conclusively shows that a carbonyl is present rather than a Thicarbonyl

Figure A 84: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate X



Retention time (min)	**Name**
4.06	Methyl bromothiolformate
6.33	4-Formylmorpholine
6.79	2,5-Dimbromohexane
6.89	2,5-Dimbromohexane
8.06	4-Thioformylmorpholine
10.00	*O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate
10.07	*O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate

Figure A 85: Mass Spectrum of *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate



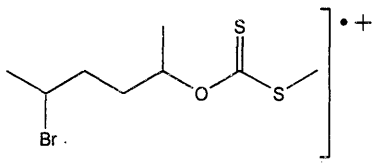
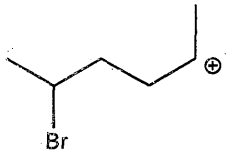
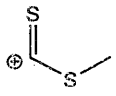
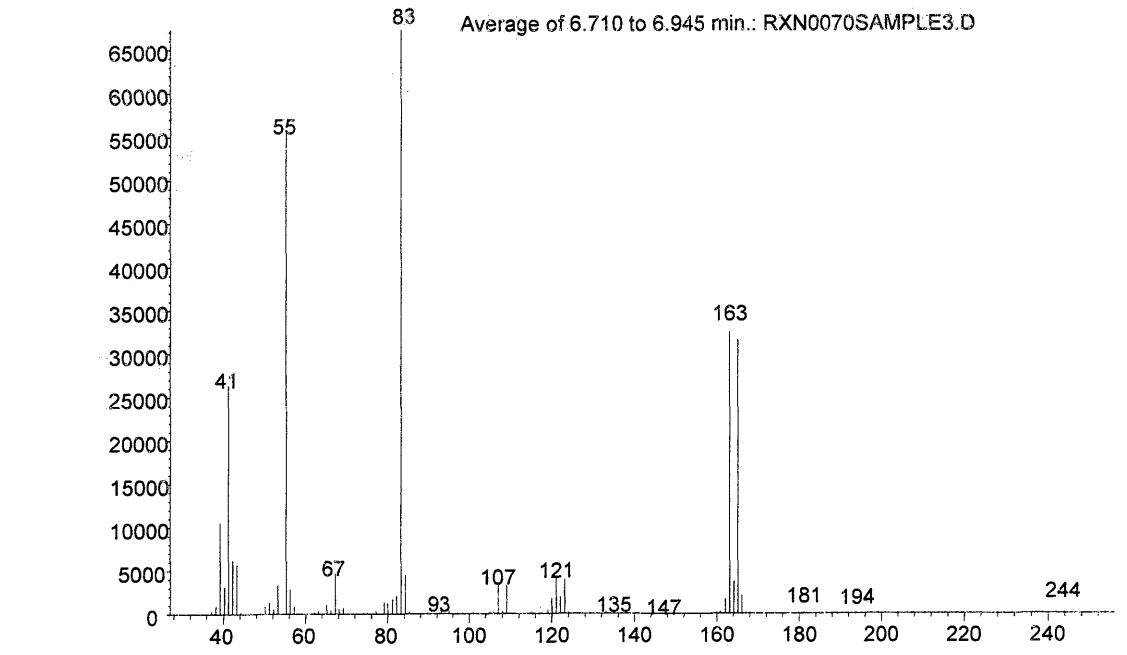
Mass	Ion / Radical	
272		Molecular Ion
163/165		
91		

Figure A 86: Mass Spectrum of 2,5-Dibromohexane



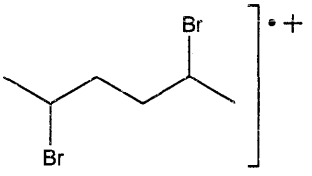
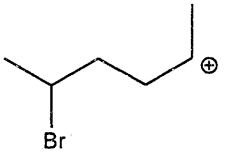
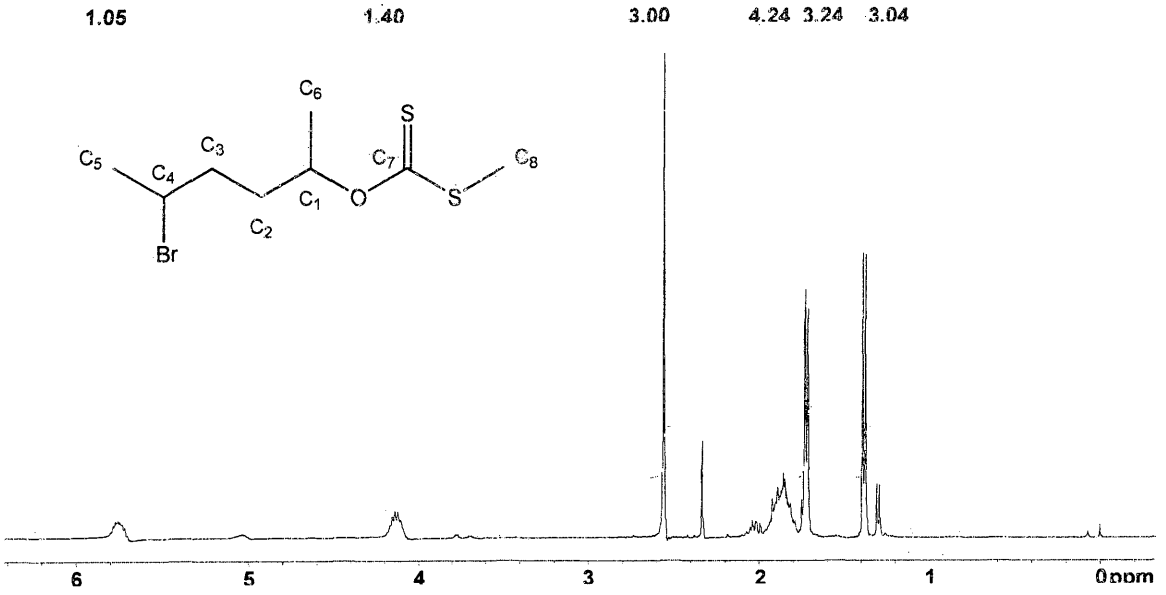
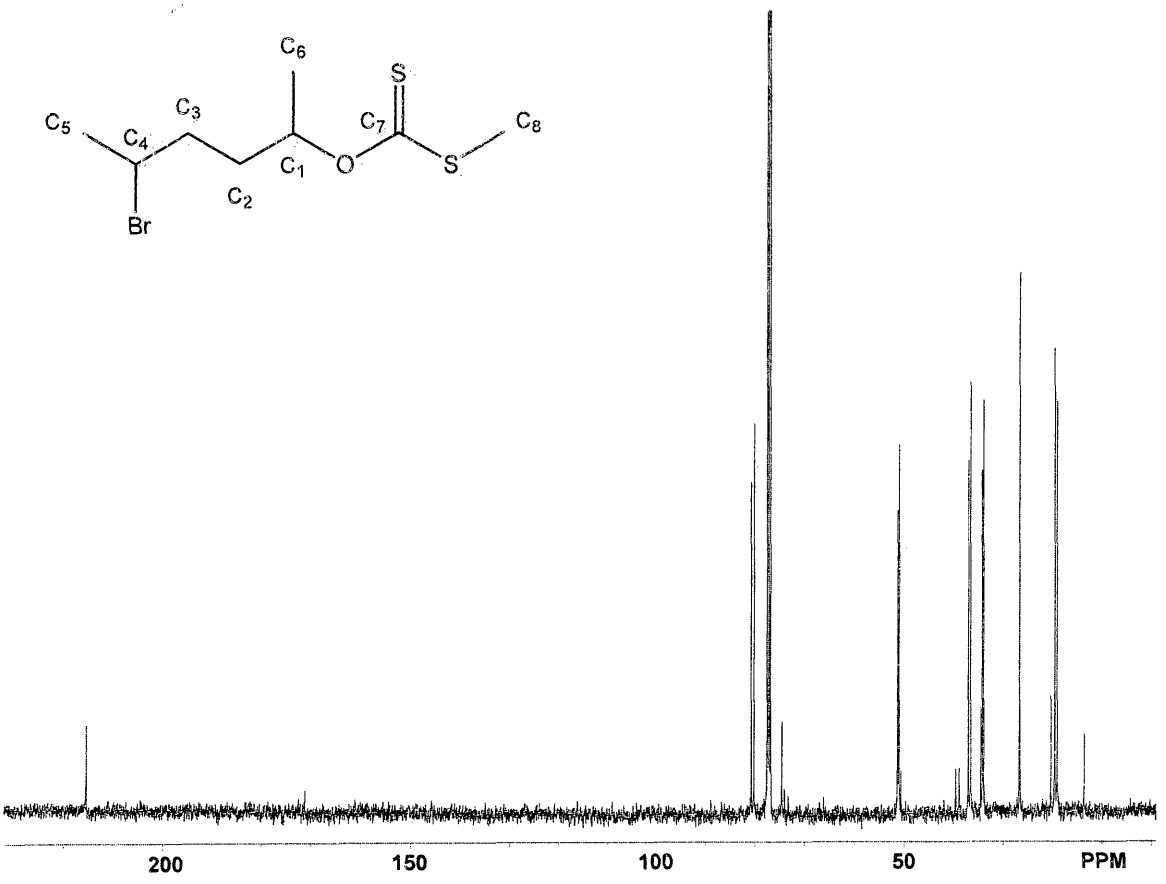
Mass	Ion / Radical	
244		Molecular Ion
163/165		

Figure A 87: ^{1}H-NMR of *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate



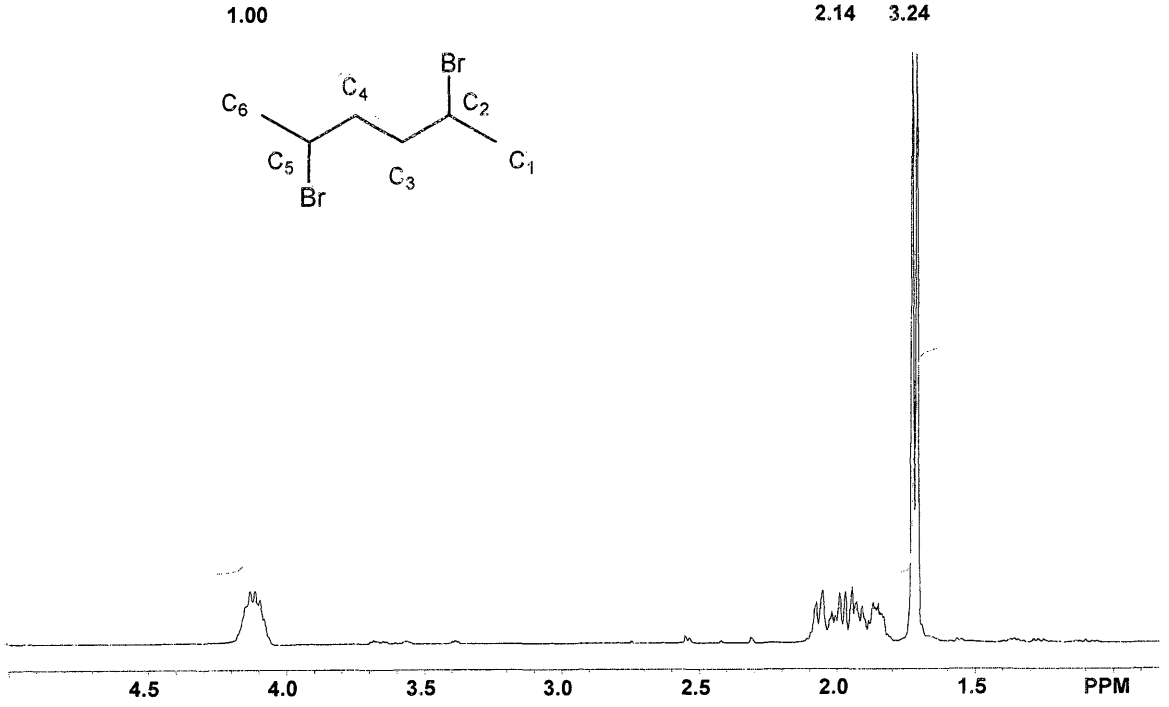
Parent Carbon	Multiplicity	Hz	ppm	Relative Intensity
C_6	Doublet	**550.46**	**1.376**	**60.439**
		556.73	**1.391**	**60.483**
C_5	Doublet	**685.15**	**1.712**	**48.798**
		691.73	**1.729**	**52.596**
C_2,C_3	Multiplet	725.73	1.814	7.254
		738.95	1.847	12.090
		741.84	**1.854**	**13.459**
		755.05	1.887	10.376
		768.61	1.921	8.006
C_8	Singlet	**1023.07**	**2.557**	**101.429**
C_4	Multiplet	1643.25	4.107	3.805
		1649.11	4.121	5.535
		1655.77	**4.138**	**5.698**
		1662.51	4.155	4.555
		1668.65	4.170	2.906
C_1	Multiplet	2272.33	5.679	-0.363
		2281.02	5.701	0.947
		2287.52	5.717	2.338
		2293.04	5.731	3.016
		2298.91	**5.745**	**3.484**
		2302.85	5.755	3.912
		2307.60	5.767	3.522
		2313.38	5.782	2.795
		2319.75	5.798	1.454

Figure A 88: ^{13}C-NMR of *O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate



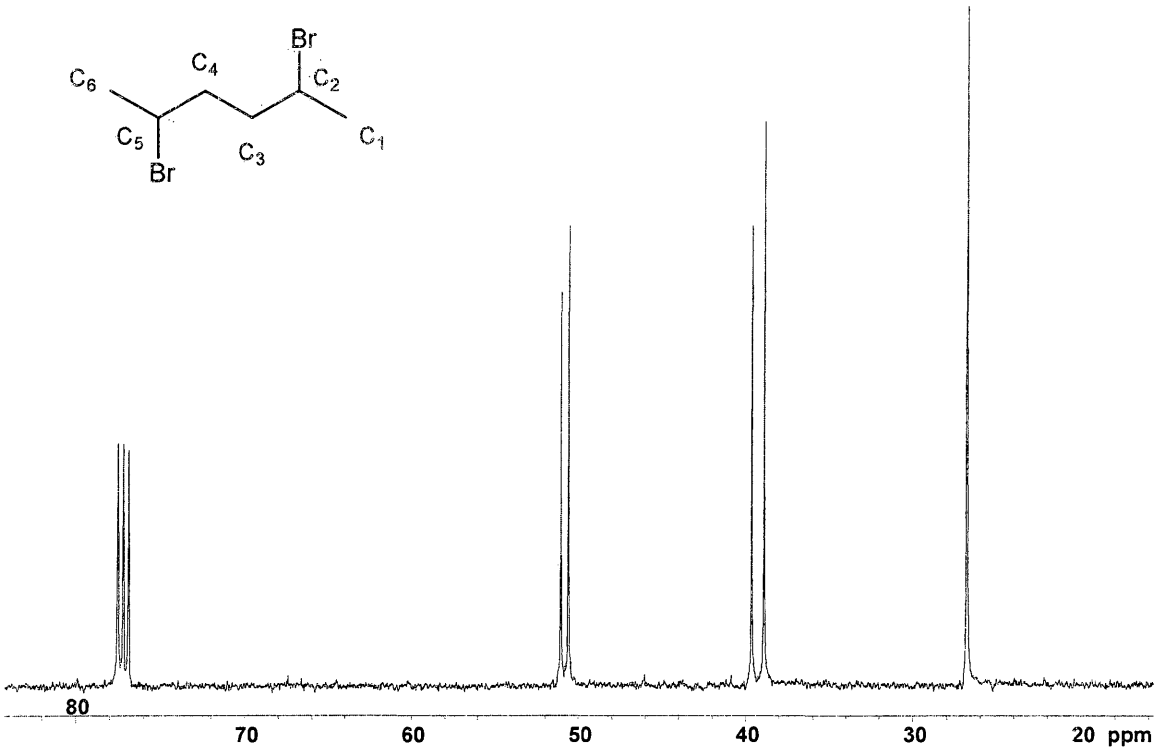
Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1927.14	19.152	50.159
2	C_6	1973.96	19.617	52.448
3	C_6	1977.25	19.650	58.193
4	C_5	2691.03	26.744	67.321
5	C_5	2693.70	26.770	65.840
6	C_2	3420.48	33.993	52.565
7	C_2	3453.72	34.323	42.231
8	C_3	3688.22	36.654	54.821
9	C_3	3736.46	37.133	44.043
10	C_4	5137.74	51.059	46.357
11	C_4	5163.59	51.316	38.201
12	C_1	8067.13	80.172	48.557
13	C_1	8122.86	80.726	41.917
14	C_7	21675.92	215.418	7.928
15	C_7	21683.61	215.494	10.689

Figure A 89: ^{1}H-NMR of 2,5-Dibromohexane



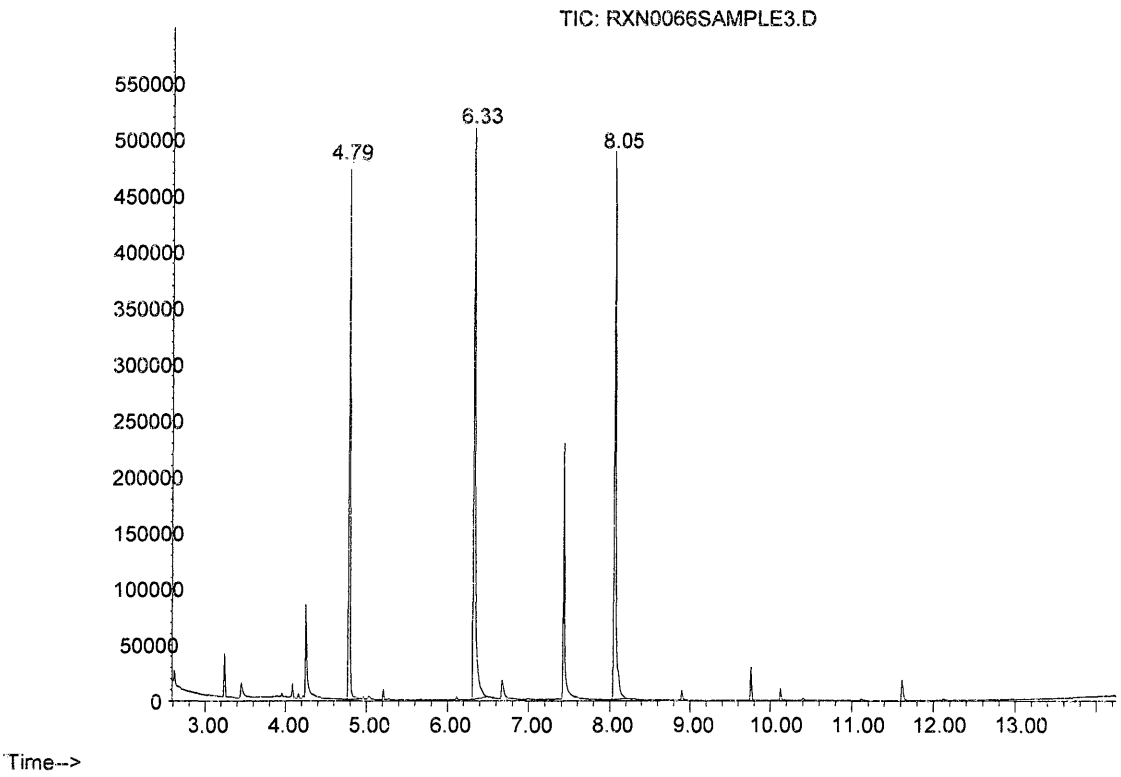
Parent Carbon	Multiplicity	Hz	ppm	Relative Intensity
C_1,C_6	Doublet	692.16	1.730	101.059
		698.81	1.746	99.496
C_3,C_4	Multiplet	739.00	1.847	4.453
		748.05	1.870	6.659
		755.61	1.888	6.730
		760.95	1.902	3.612
		771.08	1.927	6.110
		779.29	1.948	6.969
		785.87	1.964	9.421
		795.83	1.989	9.557
		803.90	2.009	8.441
		809.35	2.023	4.302
		814.92	2.037	5.200
		817.93	2.044	3.752
		828.06	2.069	8.757
		837.48	2.093	6.689
		844.75	2.111	1.338
C_2,C_5	Multiplet	1634.07	4.084	1.243
		1640.25	4.099	4.382
		1646.77	4.116	7.533
		1653.84	4.133	9.048
		1661.97	4.154	9.018
		1668.67	4.170	6.423

Figure A 90: ^{13}C-NMR of 2,5-Dibromo-hexane



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_1,C_6	2698.71	26.820	100.582
2	C_1,C_6	2700.74	26.840	97.018
3	C_3,C_4	3919.94	38.957	86.820
4	C_3,C_4	3993.42	39.687	71.880
5	C_2,C_5	5095.13	50.636	70.759
6	C_2,C_5	5140.38	51.086	60.713

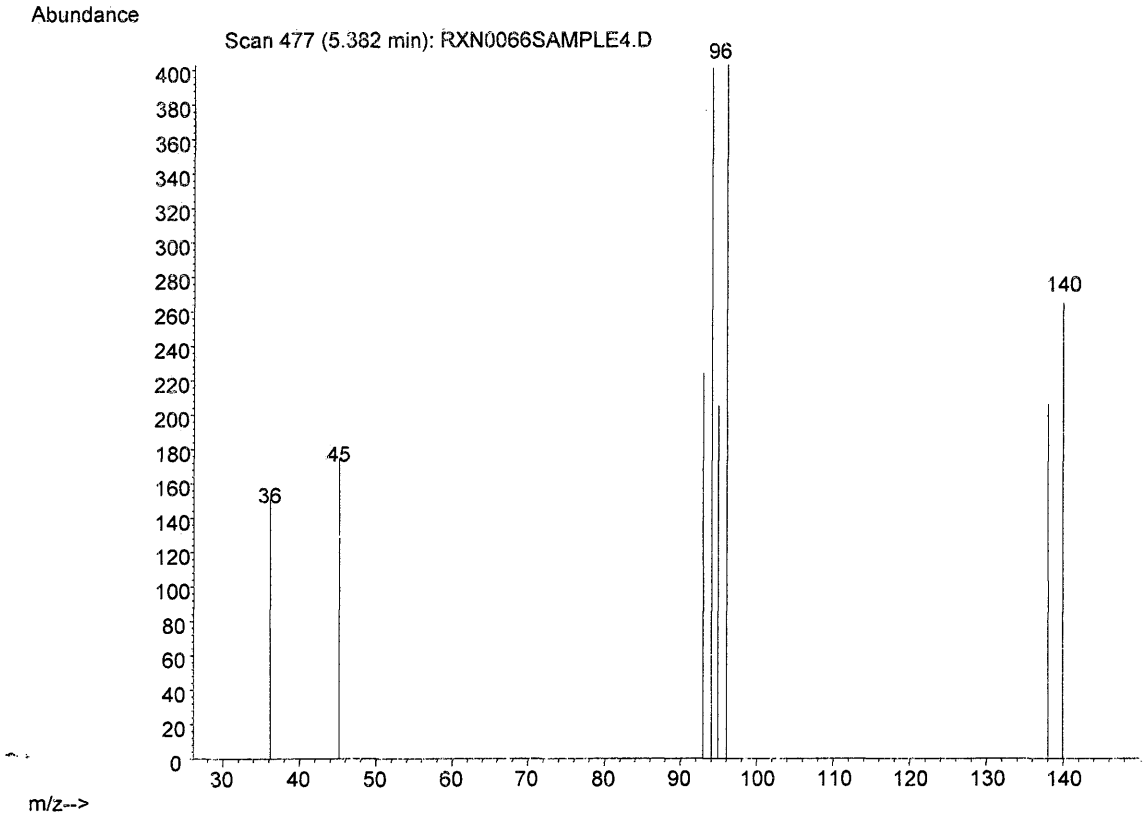
Figure A 91: Gas Chromatograph of 1.5 Vilsmeier Equivalent Deprotection of Xanthate XI

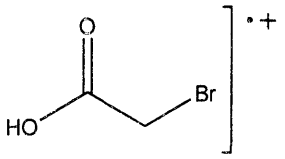
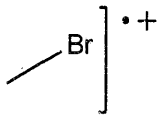
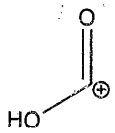


Retention time (min)	**Name**
4.79	Ethyl bromothiolformate
5.38[a]	2-Bromoethanoic acid
6.33	4-Formylmorpholine
8.05	4-Thioformylmorpholine

[a]There was only a trace amount of 2-Bromo-ethanoic acid observed, so a peak is not apparent

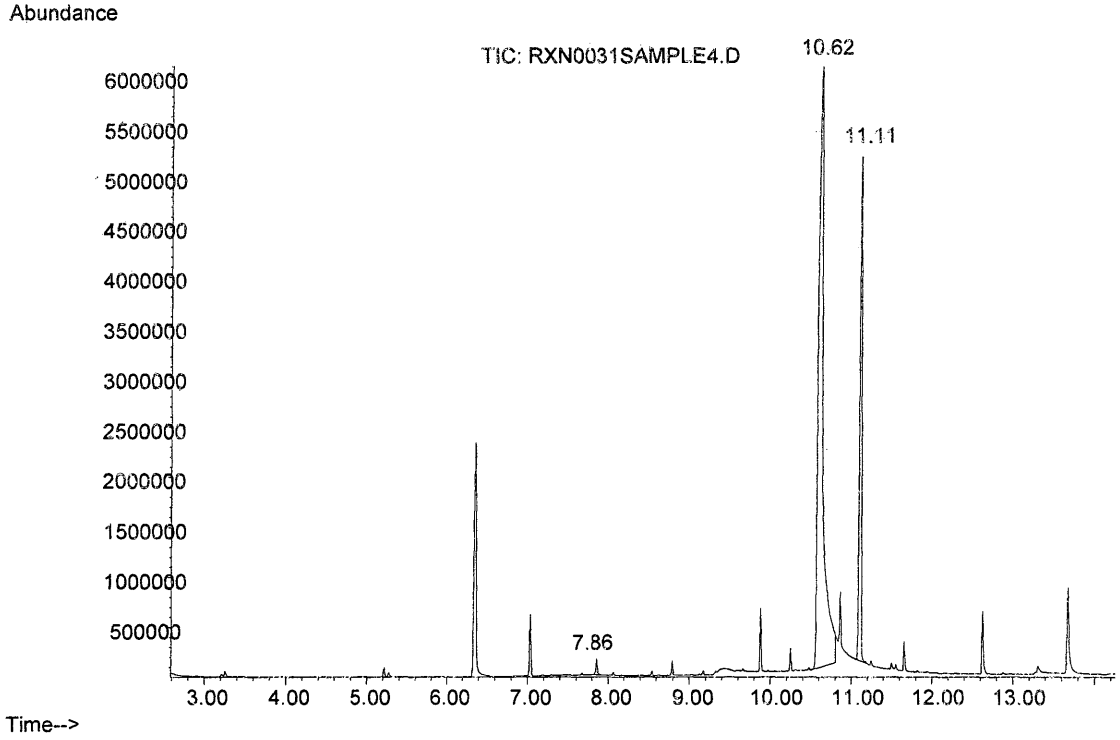
Figure A 92: Mass Spectrum of 2-Bromoethanoic acid[a]



Mass	Ion / Radical	
138/140		Molecular Ion
96/94		
45		

[a] 2-Bromo-ethanoic acid was present in GC chromatograph in only trace amounts, which may account for the scarcity of fragment peaks

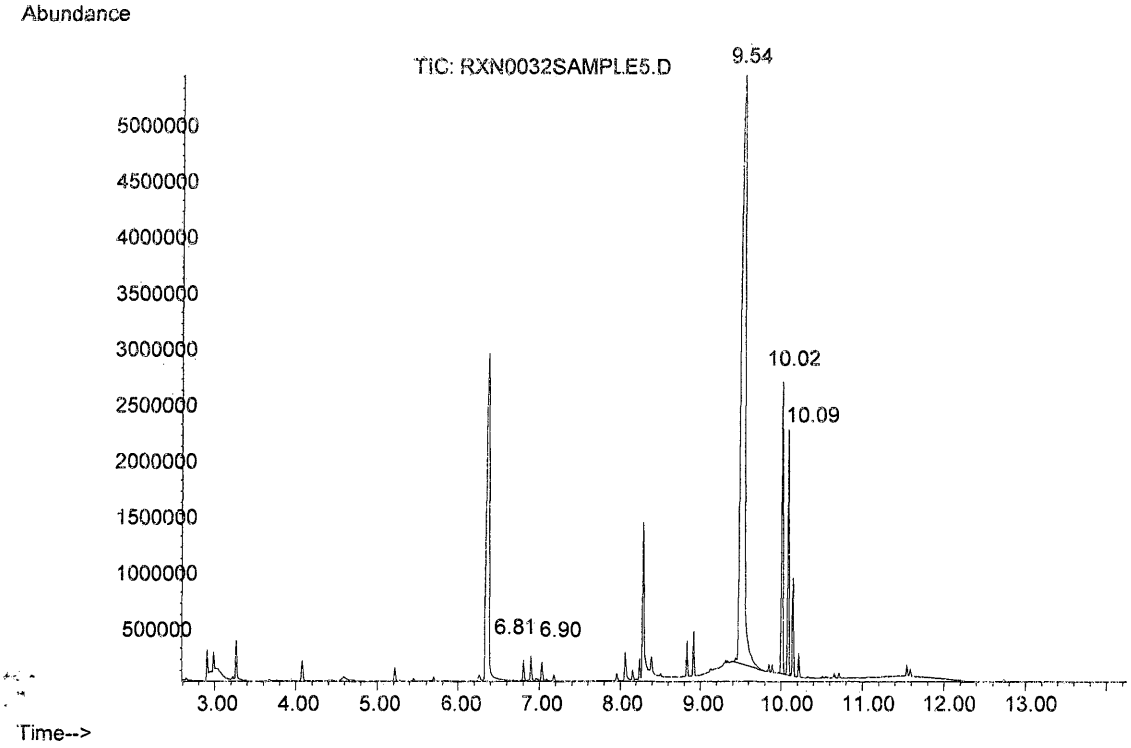
Figure A 93: Gas Chromatograph from Chemoselective Study of VII[a]



Retention time (min)	**Name**
7.86	1,6-Dimbromohexane
10.62	**VII**
11.11	*O*-(6-bromohexyl)-*S*-methylxanthate

[a]Large number of impurities are due to degradation that occurred during the distillation of VII. Latter reactions used chromatography for isolation.

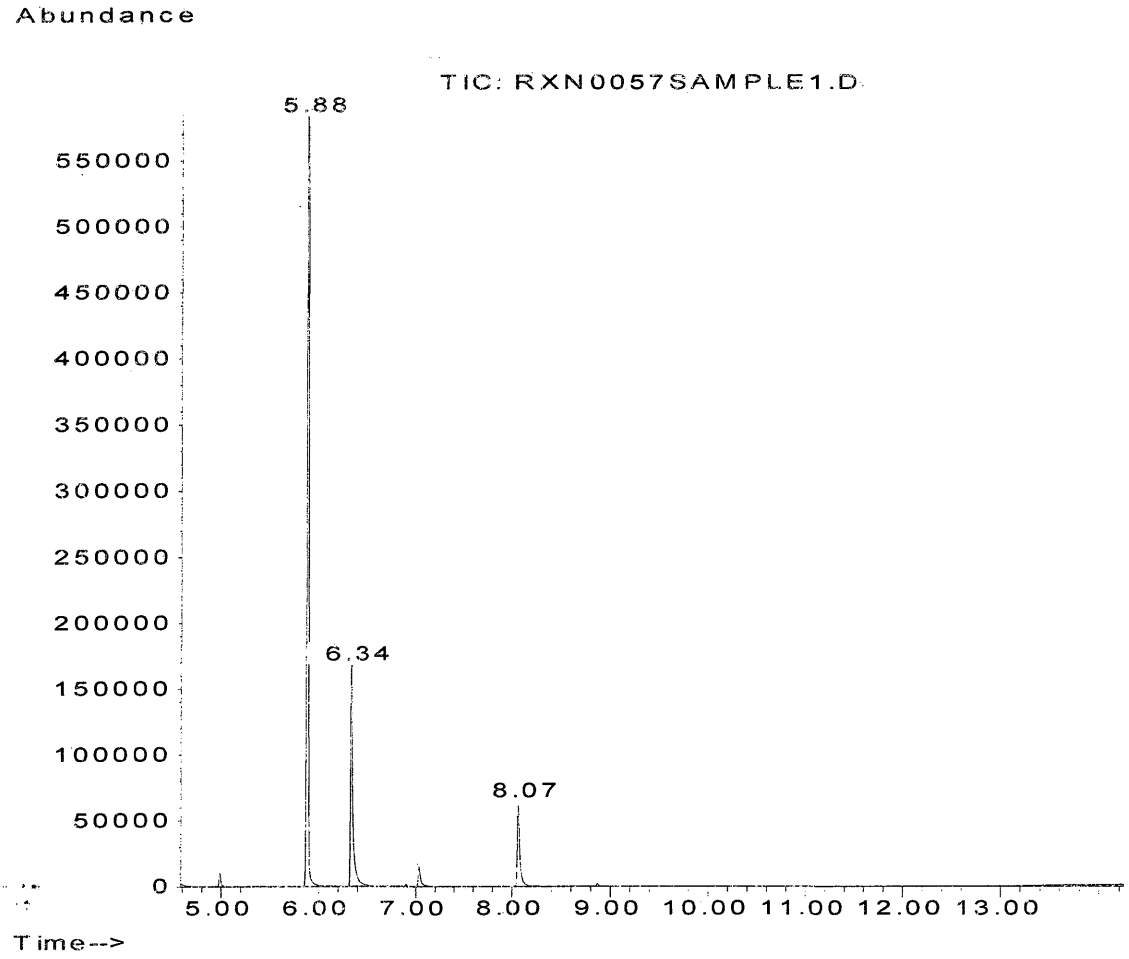
Figure A 94: Gas Chromatograph from Chemoselective Study of X[a]



Retention time (min)	**Name**
6.81	2,5-Dimbromohexane
6.90	2,5-Dimbromohexane
9.54	**X**
10.02	*O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate
10.09	*O*-(4-bromo-1-methylpentyl)-*S*-methylxanthate

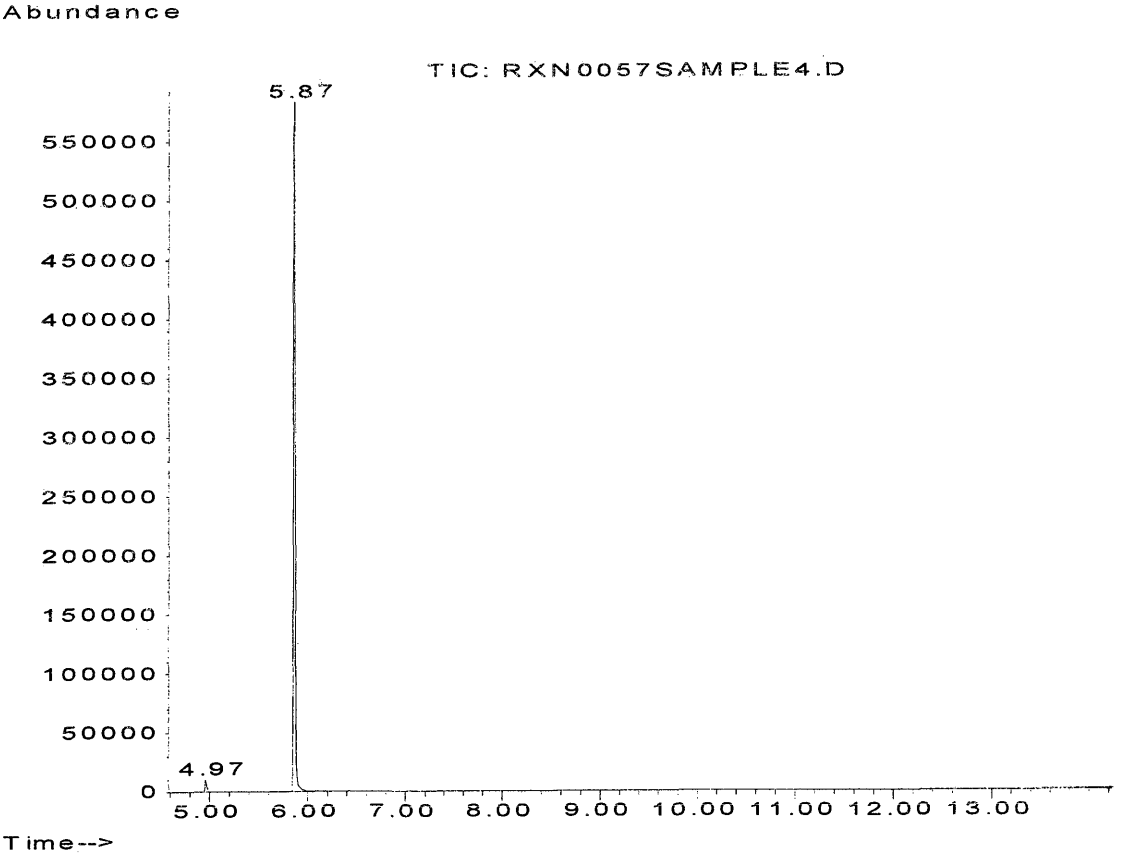
[a]Large number of impurities are due to degradation that occurred during the distillation of X. Latter reactions used chromatography for isolation.

Figure A 95: Gas Chromatograph of Methyl bromodithioformate Synthesis Reaction Pot



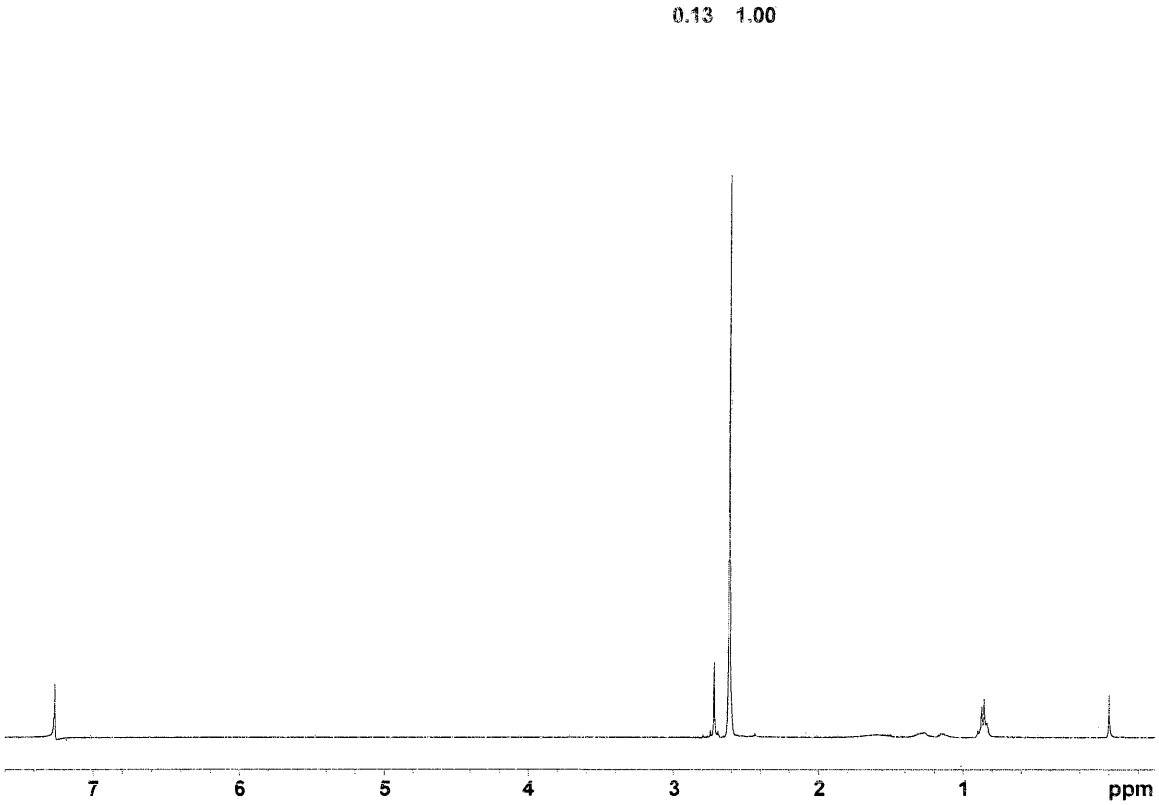
Retention time (min)	Name
4.97	Methyl chlorodithiolformate
5.88	Methyl bromodithioformate
6.34	4-Formylmorpholine
7.07	Dimethyl trithiocarbonate
8.06	4-Thioformyl-morpholine

Figure A 96: Gas Chromatograph of Methyl bromodithioformate Synthesis Final Product



Retention time (min)	**Name**
4.97	Methyl chlorodithiolformate
5.87	Methyl bromodithioformate

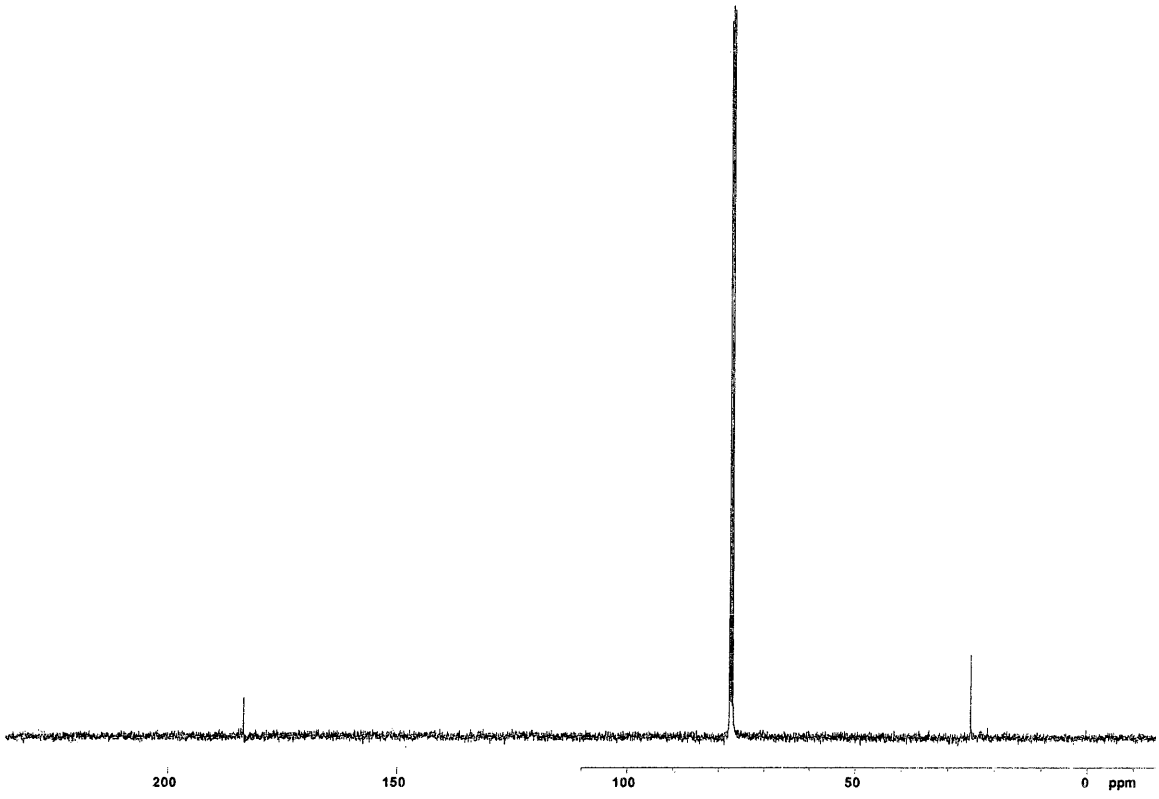
Figure A 97: ^{1}H-NMR of Methyl-bromo-dithioformate[a]



Compound	Hz	ppm	Relative Intensity
Methyl-bromo-dithioformate	1047.37	2.618	102.616
Methyl-chloro-dithioformate	1087.61	2.718	13.040

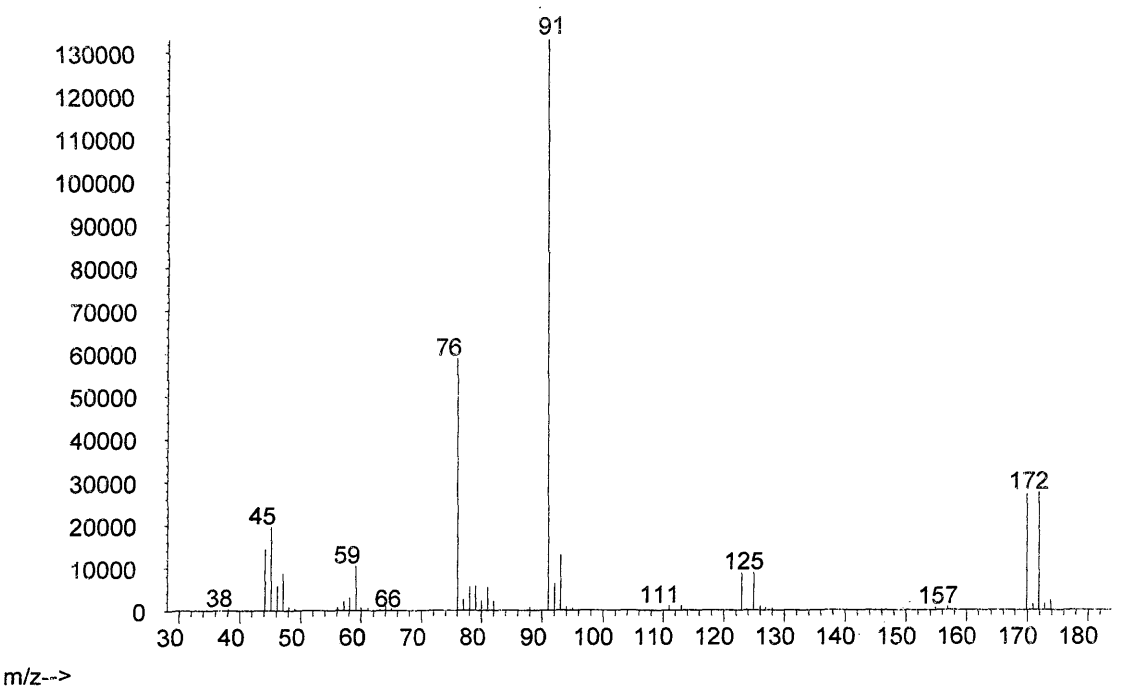
[a]The singlets are the signals from the corresponding methyl protons

Figure A 98: ^{13}C-NMR of Methyl-bromo-dithioformate



Peak	Carbon	Hz	ppm	Relative Intensity
1	C_1	2502.80	24.873	0.637
2	C_2	18469.72	183.554	5.604

Figure A 99: Mass Spectrum of Methyl bromodithioformate



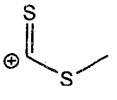
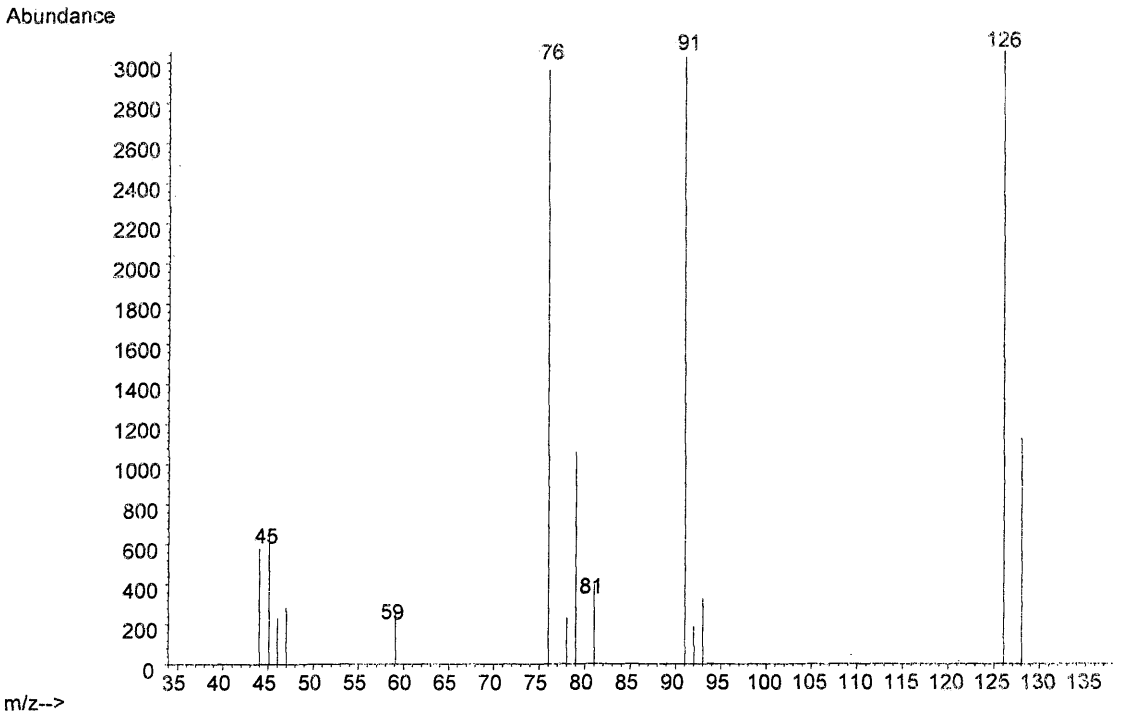
Mass	Ion / Radical
172/170	Molecular Ion
125/123	
91	

Figure A 100: Mass Spectrum of Methyl chlorodithioformate



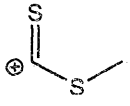
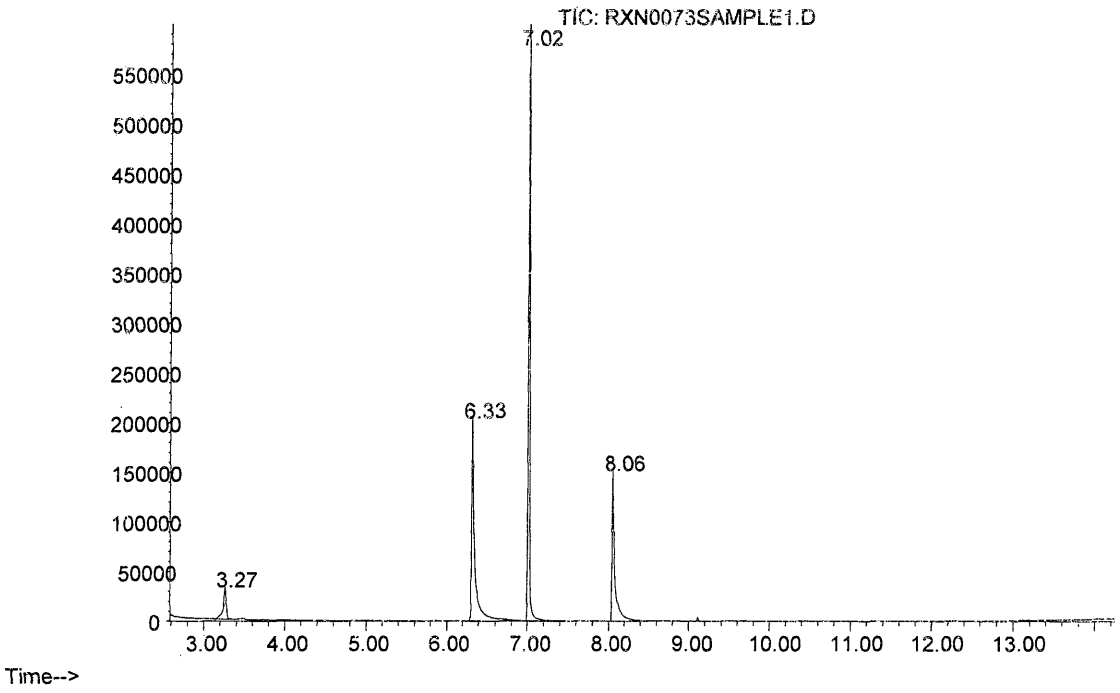
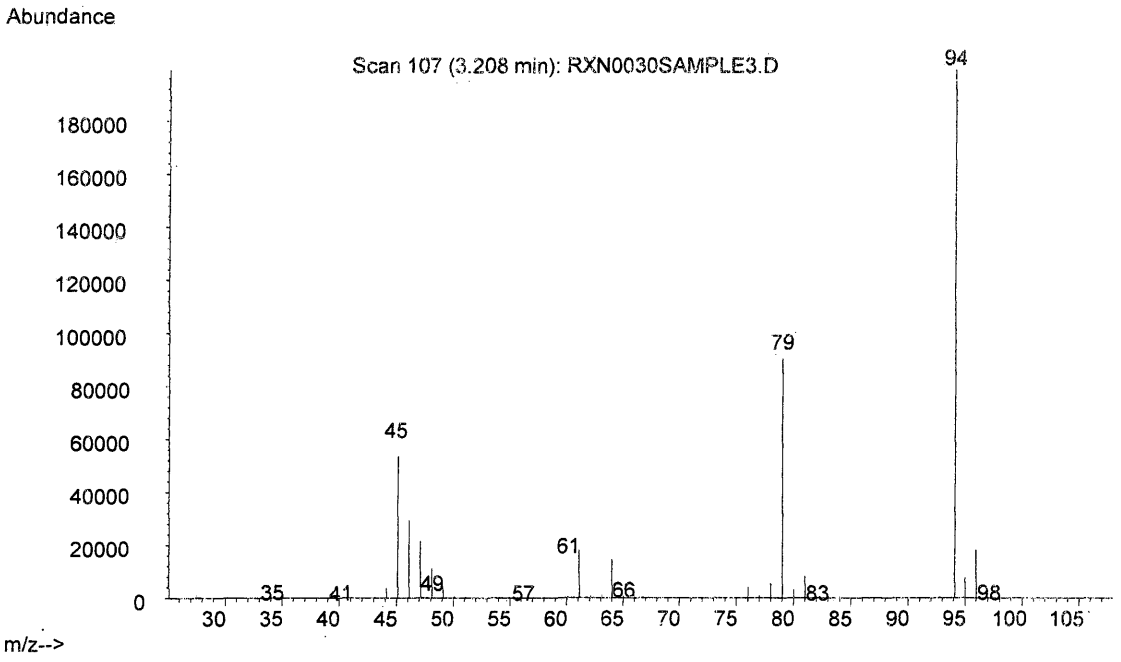
Mass	**Ion / Radical**
126	Molecular Ion
91	

Figure A 101: Gas Chromatograph of Failed Methyl bromodithioformate Synthesis



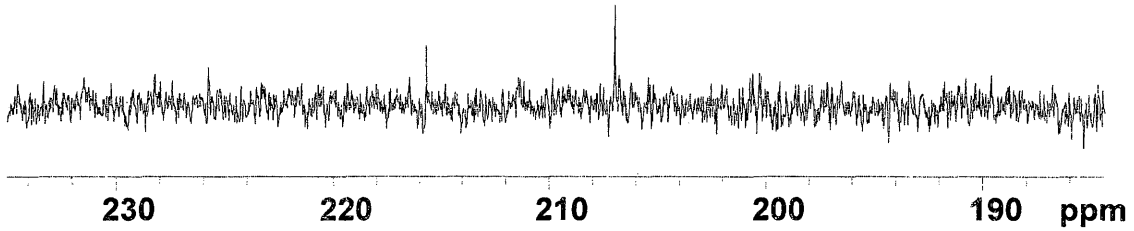
Retention time (min)	Name
3.27	1,2-Dimethyl disulfane
6.34	4-Formylmorpholine
7.02	Dimethyl trithiocarbonate
8.06	4-Thioformyl-morpholine

Figure A 102: Mass Spectrum of 1,2-Dimethyl disulfane



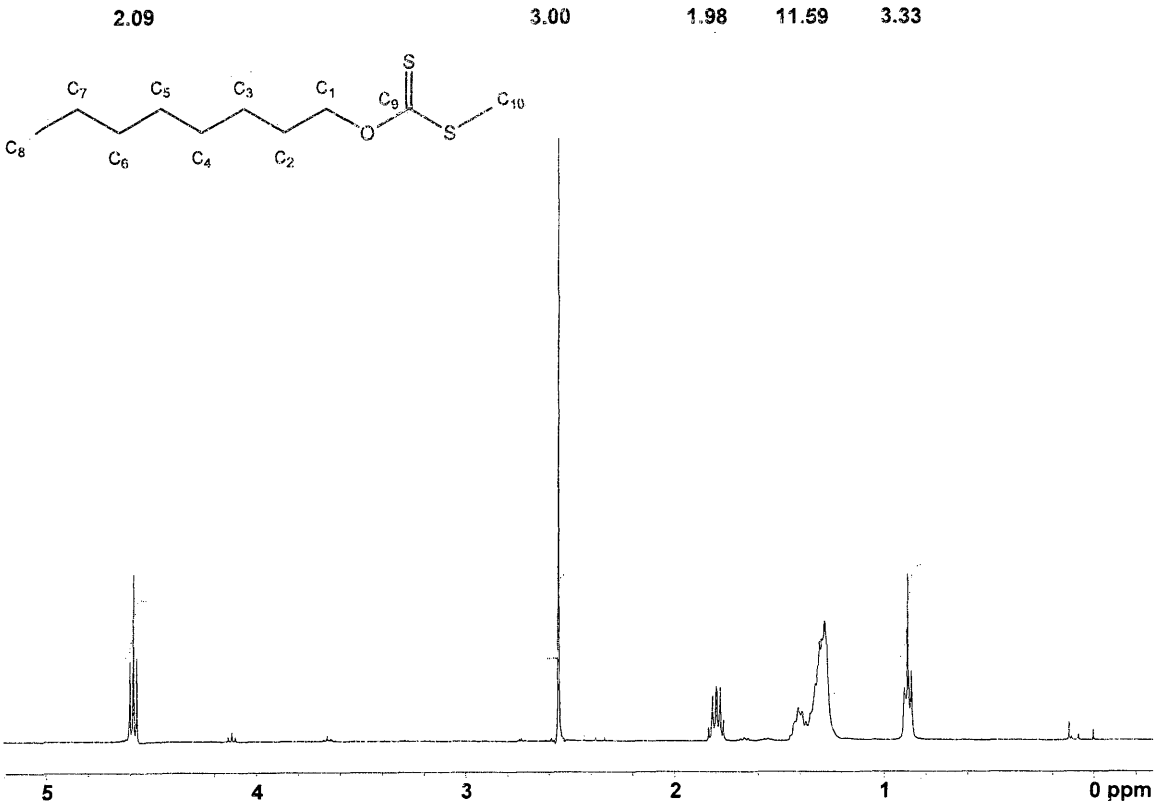
Mass	Ion / Radical
94	Molecular Ion
79	

Figure A 103: ^{13}C-NMR of Failed Methyl bromodithioformate Synthesis



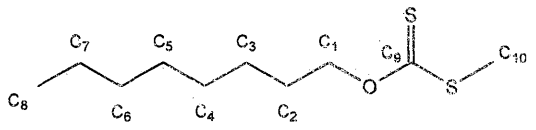
Peak	Compound	Hz	ppm	Relative Intensity
1	Acetone	20824.20	206.953	1.781
2	Dimethyl trithiocarbonate	21702.37	215.681	1.129
3	*Bis*(methylthiothiocarbonyl)sulfane	22716.99	225.764	0.751

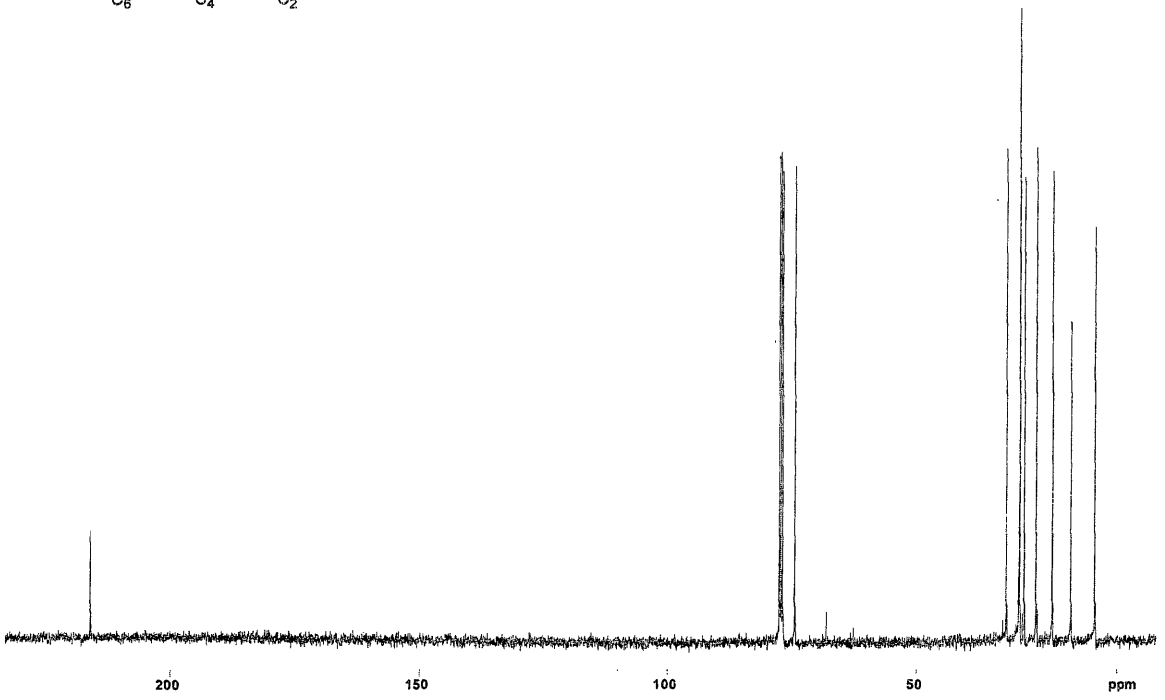
Figure A 104: ^{1}H-NMR of *O*-Octyl-*S*-methyl-xanthate



Parent Carbon	Multiplicity	Hz	ppm	Relative Intensity
C_8	Triplet	347.65	0.869	11.536
		354.71	0.886	28.315
		361.35	0.903	8.766
C_3- C_6	Multiplet	512.61	1.281	19.880
C_7	Quintet	548.16	1.370	3.103
		555.55	1.388	4.736
		563.38	1.408	5.362
		570.10	1.425	3.048
		576.76	1.441	0.791
C_2	Quintet	705.56	1.763	3.445
		712.01	1.779	9.138
		719.80	1.799	9.211
		727.00	1.817	7.471
		733.50	1.833	2.226
C_{10}	Singlet	1023.12	2.557	109.056
C_1	Triplet	1828.78	4.570	14.872
		1835.36	4.587	29.172
		1841.95	4.603	13.401

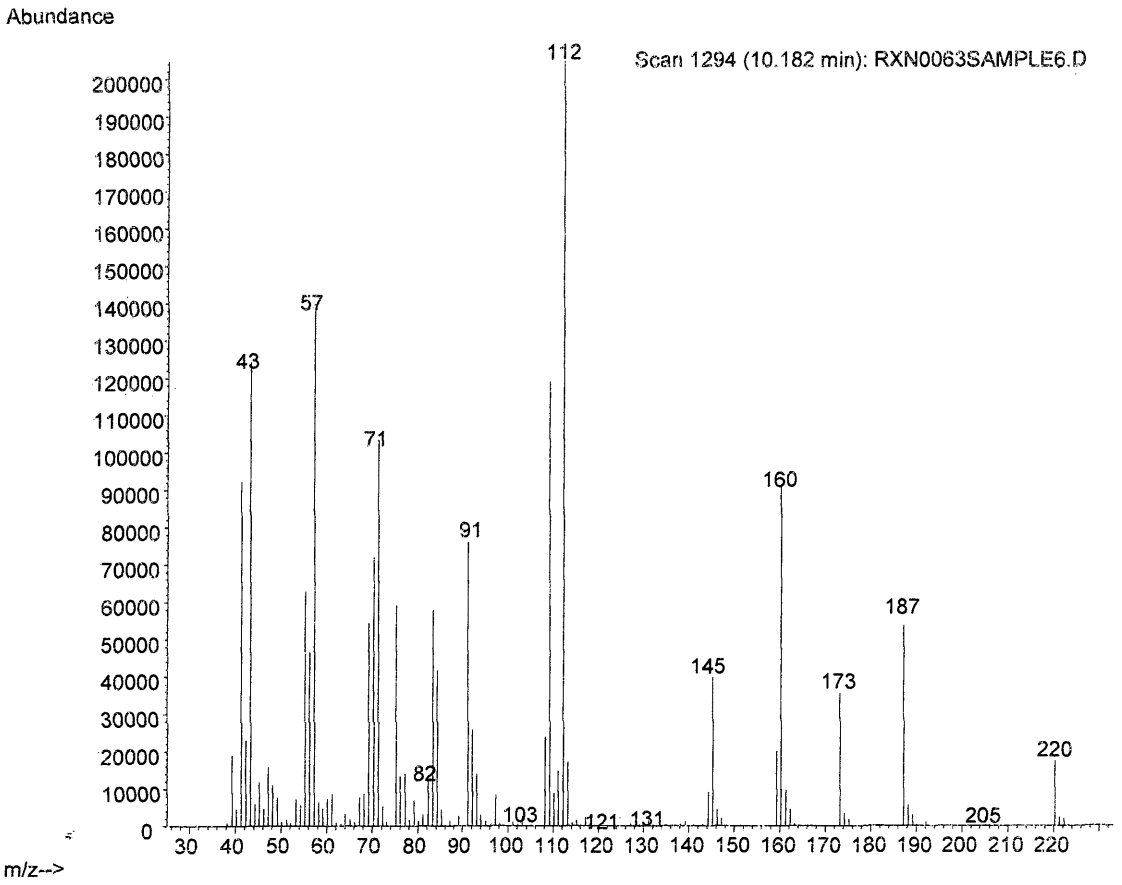
Figure A 105: ^{13}C-NMR of *O*-Octyl-*S*-methyl-xanthate

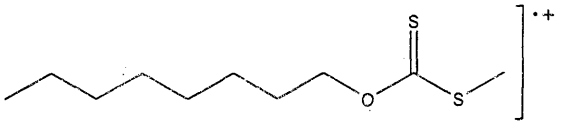
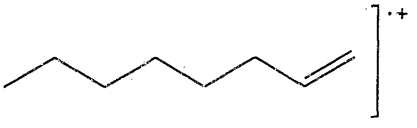
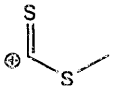




Peak	Carbon	Hz	ppm	Relative Intensity
1	C_8	1446.97	14.380	64.451
2	C_{10}	1929.82	19.179	49.673
3	C_7	2304.70	22.904	76.664
4	C_3	2631.88	26.156	80.420
5	C_2	2867.67	28.499	74.634
6	C_4	2958.52	29.402	91.445
7	C_5	2962.53	29.442	101.663
8	C_6	3221.25	32.013	80.529
9	C_1	7493.32	74.469	76.946
10	C_9	21726.36	215.919	17.264

Figure A 106: Mass Spectrum of *O*-Octyl-*S*-methyl-xanthate



Mass	Ion / Radical	
220		Molecular Ion
112		
91		

Vita

Matthew Hobson Jones

The author was bon in Virginia Beach, Virginia, on February 1, 1985. He graduated from Christchurch School in Christchurch, Virginia in 2003 and then moved on to the College of William and Mary in Williamsburg where he graduated with a B.S. in Chemistry in December of 2006. In January of 2007 Matthew began work as a graduate student in the Chemistry Department at the College of William and Mary. After completing his M.S. degree in Chemistry he will move on to the University of Virginia to pursue a degree in Medicine.